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EFFECTIVENESS OF METHYLPREDNISOLONE WITH METHOXYPHENAMINE IN RESPIRATORY ALLERGY

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BRONCHIAL asthma is a recurrent illness precipitated by many factors, and characterized by expiratory dyspnea with an audible wheeze. There is edema of the bronchial mucosa, a heavy mucous exudate, and constriction of the bronchioles, particularly during expiration.

Since the discovery of the effectiveness of the adrenocorticosteroids, these substances have received increasing attention in the treatment of this syndrome.[1,2] Because of side effects and the occasional development of refractoriness to cortisone and hydrocortisone, interest in new compounds prednisone, prednisolone, methylprednisolone, and others that show promise of exhibiting improved activity, is continuing.[3-12] In the development of these new steroids, the objectives have been not only to increase potency so as to reduce the required steroid dosage, particularly during maintenance therapy; but also, and more important, to eliminate or significantly reduce mineralo-corticoid and other unwanted side effects. Methylprednisolone (Medrol®) has shown considerable promise in regard to each of these aims.[11,13-15]

To further reduce the dose, it is customary to use bronchodilators in conjunction with adrenal steroids—in controlling the acute asthmatic attack and during maintenance therapy. Methoxyphenamine (Orthoxine®) is a well-tolerated bronchodilator, which is well-suited to long term therapy.

The changes in allergic rhinitis are similar to those of bronchial asthma, except for the constrictive component in the latter. For this reason, adrenal

Methylprednisolone and methoxyphenamine (labeled Medrol with Orthoxine) and coded medicaments were supplied by The Upjohn Company. This study was supported by a grant from The Upjohn Company.

*Registered trade mark, The Upjohn Company.

steroids can be successfully used in the treatment of severe allergic rhinitis, Bronchodilators are also used in treating this condition, because of their decongestant effect on the mucosa of the entire respiratory tract.

The purpose of this paper is to record the data obtained in a clinical study of the effectiveness of tablets containing methylprednisolone and methoxyphenamine (supplied as Medrol with Orthoxine) in the treatment of bronchial asthma and allergic rhinitis.

METHODS

One hundred and six patients were treated with tablets containing known combinations of methylprednisolone and methoxyphenamine hydrochloride. Seventy of the patients had bronchial asthma, seventeen patients had a combination of bronchial asthma and allergic rhinitis, and nineteen patients had allergic rhinitis only. The Medrol and Orthoxine were supplied in tablets containing both drugs but in two combinations. Each tablet contained 75 mg of methoxyphenamine combined with either 2 mg or 4 mg of methylprednisolone. The patients received from 20 to 200 tablets, having been given at least a sufficient amount for a trial of five days. Usually a t.i.d. or q.i.d. dosage schedule was used, but a few patients needed only two tablets daily.

TABLE I. RESULTS OF TREATMENT WITH KNOWN COMBINATIONS OF MEDROL WITH ORTHOXINE

Medication Medrol Orthoxine	Number of Patients	Results Satisfactory	Less Steroid Needed	More Steroid Needed
2 mg 75 mg	40	37 (92.5%)	8	3
4 mg 75 mg	80	67 (84%)	12	2
Totals	120	104 (87%)	20	5

An additional eighty-five patients were treated in 130 trials with tablets identified only by code numbers. Twenty-seven of these patients had asthma, forty-three patients had asthma and allergic rhinitis, and fifteen patients had allergic rhinitis alone. Some of the tablets used to treat this group contained formulae similar to those in the tablets used in the first group. Others contained different amounts of methylprednisolone, a placebo, or methoxyphenamine alone. Ordinarily one tablet was given t.i.d. or q.i.d., but occasionally a b.i.d. dosage schedule was used.

In all cases, the drugs were rated with reference to three criteria: side effects, subjective control of symptoms, and objective control of the disease.

The vital capacity was measured before and after therapy in forty-two patients on known combinations of Medrol with Orthoxine. These included twelve patients taking Medrol 2 mg with Orthoxine and twenty-nine patients taking Medrol 4 mg with Orthoxine. Six patients in the blind label group also had their vital capacities determined. In each instance,

the total vital capacity and the vital capacity over a brief interval of time (one-half second) were determined simultaneously.

Calculations of percentages and means were made with the use of a slide rule.

RESULTS

The results of therapy in the 106 patients taking known combinations of Medrol and Orthoxine are indicated in Table I. There were 120 clinical trials as several patients were placed on more than one combination.

Ninety of the patients (85 per cent) felt that the tablets satisfactorily controlled their disease and sixteen (15 per cent) thought the tablets were unsatisfactory. In comparing the effectiveness of the formulation with the steroid used alone, it was felt that the steroid alone was better in five 4.7 per cent); the combination was equal to the steroid in sixty-two (58.5 per cent), and the combination was better in thirty-nine (36.8 per cent) of the patients.

TABLE II. RESULTS OF TREATMENT USING CODED MEDICAMENTS

Medication	Number of Patients	Results Satisfactory
Medrol 1 mg	17	11 (65%)
Medrol 2 mg	15	10 (67%)
Medrol 4 mg	18	15 (83%)
Placebo	12	3 (25%)
Orthoxine 75 mg	15	9 (60%)
Medrol 1 mg with orthoxine 75 mg	18	14 (78%)
Medrol 2 mg with orthoxine 75 mg	17	15 (88%)
Medrol 4 mg with orthoxine 75 mg	18	16 (89%)
Totals	130	93

There was excellent cough control in twenty-three patients, relief of asthma in seventy-seven, and relief of allergic rhinitis in thirty-nine. This total is greater than 106 because some patients had more than one condition. Of thirty-nine patients with a cough only three (7.7 per cent) failed to have improvement.

One patient with allergic rhinitis and asthma did well on three schedules. Initially this patient took 2 mg Medrol with Orthoxine t.i.d., then he was placed on Medrol 4 mg with Orthoxine q.i.d. during an aggravation of symptoms associated with an infection, and subsequent to the infection he was controlled on Medrol 2 mg with Orthoxine b.i.d. A patient with allergic rhinitis initially could not be controlled on Medrol 4 mg with Orthoxine q.i.d., but on maintenance was controlled with Medrol 4 mg with Orthoxine b.i.d. and subsequently with Medrol 2 mg with Orthoxine b.i.d.

The results of the use of tablets identified only by code numbers are recorded in Table II. The placebo was the least satisfactory of the medicaments, and the response to equivalent doses of the steroid was enhanced by the presence of Orthoxine.

One or more mild side effects were noted in twenty-two of the 105 patients on known combinations of Medrol with Orthoxine. These are recorded in Table III. In Table IV, the side effects occurring in nineteen patients in the double blind group are indicated. Nervousness occurred most often. It was complained of by patients on all medicaments, including the placebo. There were no serious side effects.

TABLE III. SIDE EFFECTS WITH KNOWN COMBINATIONS OF MEDROL WITH ORTHOXINE

	Medrol 2 mg* with Orthoxine	Medrol 4 mg** with Orthoxine
Nervousness	7 (17.5%)	9 (11%)
G I distress	3 (7.5%)	2 (2.5%)
Moon facies	1 (2.5%)	1 (1.25%)
Urinary symptoms	1 (2.5%)	1 (1.25%)
Totals	12 (30%)	13 (16%)

*Forty clinical trials.
**Eighty clinical trials.

Of the forty-two patients on known combinations of Medrol with Orthoxine whose vital capacity was measured, all except two patients on Medrol 4 mg with Orthoxine showed an increase in vital capacity after therapy. Before treatment the total vital capacity ranged from 600-4700 with a mean value of 1720. The one-half second vital capacity was 300-1900 before treatment—the mean value was 875. After treatment the range of the total vital capacity was 700-4800, the mean 2280; the range of the one-half second vital capacity was 400-2000, the mean 1240.

TABLE IV. SIDE EFFECTS NOTED IN DOUBLE BLIND STUDY*

Side Effects	Medrol 1 mg in 17 Patients	Medrol 2 mg in 15 Patients	Medrol 4 mg in 18 Patients	Placebo in 12 Patients	Orthoxine in 15 Patients	Medrol 1 mg e Orthoxine in 18 Patients	Medrol 2 mg e Orthoxine in 17 Patients	Medrol 4 mg e Orthoxine in 18 Patients
Nervousness	4	2	1	1	3	2	3	3
Nausea	0	0	0	0	0	0	0	1
Totals	4(24%)	2(13%)	1(5.6%)	1(8.3%)	3(20%)	2(11%)	3(17.5%)	4(22%)

*130 clinical trials made with unknown medicaments.

The six patients participating in similar studies in the blind label group were all found to be taking a combination of Medrol with Orthoxine: Medrol 1 mg with Orthoxine, one patient; Medrol 2 mg with Orthoxine, two patients; and Medrol 4 mg with Orthoxine, four patients. The values of the before treatment studies were: total vital capacity 1200-2600, mean 1935; ½ second vital capacity 400-1600, mean 1000. Following treatment the total vital capacity ranged from 1400-3600, the mean 2480; ½ second vital capacity 600-2000, the mean 1415.

SUMMARY AND COMMENT

Two studies of the use of methylprednisolone with methoxyphenamine (supplied as Medrol with Orthoxine) in respiratory allergies are reported. In 120 clinical trials using known doses of Medrol with Orthoxine, there were 104 satisfactory responses. In 130 clinical trials with unknown medicaments, the response to a given dose of Medrol was improved by the presence of Orthoxine. Pulmonary function, as evidenced by the total and one-half second vital capacity, was improved in forty-six of the forty-eight patients in whom these measurements were made.

The formulation of Medrol with Orthoxine is believed to be a satisfactory preparation for the treatment of respiratory allergies, particularly when maintenance therapy with adrenal steroids is indicated. In the author's experience cough control has been excellent and in many instances the maintenance dose of Medrol in the combination was lower than when Medrol alone was used.

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CLINICAL EVALUATION OF CLYSMATHANE

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THE BRONCHIAL dilating effect of theophylline ethylenediamine (aminophylline) is well established. Over twenty-five years ago Trasoff,[13] and later Efron[3] mentioned the value of this drug, and Hermann and Aynesworth[7] in 1937 reported its use in the treatment of severe asthma. Extensive additional observations on the administration,[1,4,8] mode of action,[5,6,12] and therapeutic and toxic dosage[7,11,14,15] of theophylline ethylenediamine and related xanthine compounds have been made by many investigators.

The purpose of this study was the clinical evaluation of another xanthine compound, theophylline monoethanolamine (Clysmathane®, or Fleet Theophylline rectal unit), by comparison with theophylline ethylenediamine (aminophylline), administered orally and rectally for the symptomatic relief of bronchial asthma. In assessing the relative merits of these two closely related xanthine drugs, consideration was given to their therapeutic effectiveness, promptness of action, convenience of use, incidence of systemic side effects and local irritation, and the attitude of the patients toward rectal administration of medication.

CLINICAL PROCEDURE

The studies were carried out in two periods, the first from January to May, and the second from September to December, 1959. Since the procedures and types of patients in the first and second series differed somewhat, each series will be discussed separately.

First Series

Selection of Patients.—We chose the winter-spring period for the first series because we anticipated that many patients would require maintenance relief medication more constantly, or for longer periods of time in those seasons as a result of complicating infectious processes or because they

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Clysmathane® is the registered trade name for Theophylline monoethanolamine (Fleet) in disposable units for rectal administration.

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suffered most at that time from primarily infectious asthma. Individuals with pulmonary emphysema were included whenever possible, since they ordinarily require maintenance symptomatic relief medications. Those patients with asthma only at rare intervals were excluded, as were those dependent entirely on corticosteroid drugs, unless it was found that the xanthine preparations afforded additional help or could be substituted for the hormones. This portion of the studies was carried out on fifty adult patients, ranging in age from eighteen to seventy-four (Table I) with bronchial asthma, and one with dyspnea resulting from left ventricular failure, seen in clinic and private practice.

TABLE I

Age Groups—	Under 10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	Total
Patients in first series	0	1	3	9	9	18	10	1	51
Patients in second series	1	6	10	8	9	8	2	3	47

Administration of Drugs.—According to the plan of study, all patients were to be given each of the preparations for periods of two weeks, unless symptoms of intolerance should appear or a drug or route of administration should earlier prove completely ineffective. The starting dosage and interval were to conform essentially to the indicated routine, with later adjustments in the interest of obtaining better relief or reducing side effects before condemning the drug as ineffective or untolerated. To assure complete compliance with directions, clinic patients and private patients of the lower income group were supplied the products without cost.

The following is the routine of administration and dosage of the various preparations:

Theophylline ethylenediamine (aminophylline):

A. Oral tablets, enteric coated, 200 mg (3 grains): one tablet three or four times daily.

B. Rectal suppositories, 500 mg (7½ grains): one every twelve hours, preferably night and morning. Two widely used brands of suppositories were employed, but only one brand was supplied to each patient.

C. Tablets, plain, 200 mg (3 grains): three tablets to be crushed and dissolved in 1½ ounces of water* and administered as a retention enema every twelve hours, preferably night and morning, using a soft rubber ear syringe of two ounces capacity.

Theophylline monoethanolamine:

D. One Fleet theophylline rectal unit (Clysmathane®), containing 625 mg* in 37 ml of solution, every twelve hours, preferably night and morning.

*Average delivered dosage 500 mg.

TABLE II. PATIENTS DISCONTINUING STUDIES IN FIRST SERIES

Patient	Age	Diagnosis	First Drug	Days Used	Second Drug	Days Used	Symptoms of Intolerance	Relief from Asthma
1	39	Asthmatic bronchitis	Clysmathane	5	Ent. coated oral tabs aminophylline	3	Nausea, anal irritation (a) Severe upper gastro-intestinal irritation	Good No
2.	41	Asthmatic bronchitis	Aminophylline suppositories	18	Clysmathane	7	Anal irritation (b) Unable to retain	Fair No
3.	60	Asthmatic bronchitis, emphysema	Aminophylline suppositories	5	Clysmathane	7	Unable to retain Marked ano-rectal irritation (c)	No Good
4.	58	Asthmatic bronchitis	Clysmathane	1	Ent. coated oral tabs aminophylline	1	Restlessness, nausea, insomnia (d) Restlessness, nausea tachycardia	Fair No
5.	26	Asthmatic bronchitis, allergic asthma	Aminophylline suppositories	14	Clysmathane	3	Erratic nausea Vomiting (b)	Partial Good
6.	57	Asthmatic bronchitis	Aminophylline suppositories	2			Marked ano-rectal irritation (b, e) Unable to retain	No

(a) Tolerates "Quadrinal" tablets.
(b) Tolerates "Elixophyllin."
(c) Tolerates "Choledyl" tablets.
(d) Tolerates no xanthine drugs.
(e) Tolerates aminophylline intravenously.

To minimize distortion of our results from all unpredictable or unavoidable influences, including particularly the possibility of favoring the first drug to afford relative relief, or the last because relief from it was remembered best by our patients, we employed each of the xanthine preparations in variable sequence.

Results

Patients Not Able to Complete the First Series of Studies.—Because of marked side effects, six patients could not complete the studies. Symptoms of intolerance ranged from local ano-rectal irritation to disturbances of the entire gastro-intestinal tract in five patients; in one, marked restlessness and insomnia precluded further trials. Furthermore, since five of these six experienced untoward reactions either with only two, or with the second preparation tried in the study, and one had severe side effects from only one preparation, their comparative responses to the other drugs in the series could not be determined. It is interesting to note that five patients intolerant to rectal administration of a xanthine drug could tolerate xanthine preparations by some other route (Table II).

Patients Completing the First Series of Studies.—Forty-five patients completed the studies. On the basis of their choice of the preparations relieving them most, with fewest or no side effects, in keeping with our criteria of evaluation, these patients reported results as reflected in Table III.

TABLE III. PREPARATIONS OF CHOICE REPORTED BY THE FORTY-FIVE PATIENTS COMPLETING FIRST SERIES OF STUDIES

Preparations Preferred		Number of Patients
Preferring Clysmathane		
Full strength	14	
Half strength	8	
Two-thirds strength	1	23 (51%)
Preferring equally Clysmathane and aminophylline suppositories		2
Preferring equally Clysmathane half strength and aminophylline crushed tablets as retention enemas		2
Preferring suppositories		6
Preferring aminophylline crushed tablets as retention enemas		4
Preferring enteric coated aminophylline tablets orally		4
Patients who received no definite benefit from any of the products used in the study		4
Total		45

Early in our investigations we observed side effects, occasionally of such severity that further trials were contraindicated, in several patients who otherwise obtained excellent relief from one or more of the rectally administered xanthine drugs. This therapeutic effectiveness for many patients, exhibited particularly by the aqueous preparations, suggested that reduced dosage might minimize or overcome side effects and still maintain clinical relief. With the crushed aminophylline tablets administered by retention enema, the response after dosage adjustments was still frequently unpre-

dictable, primarily because all patients did not crush the tablets with the same degree of thoroughness, resulting both in mechanical irritation by uncrushed particles, and in poor solution of the improperly crushed tablets.

The solution contained in the Clysmathane® units, however, was easily diluted with water to any desired ratio, and the unused portions could readily be replaced in the empty containers for later use. We found that dilution of the standard unit to one-half concentration frequently afforded freedom from undesirable side effects, especially restlessness and insomnia, without loss of therapeutic efficiency. Six patients naming Clysmathane® units of half strength as their first choice had originally rejected the full units on the basis of various side effects, which completely subsided with the smaller, yet clinically effective, dosage. One of these patients, however, required the full unit for severe attacks, although at the expense of insomnia, and another obtained relief without side effects with two-thirds of the standard unit. These findings confirmed excessive overlapping in the ranges of therapeutic efficiency and of intolerance in the dosage of the standard unit, at least for a number of patients. Also, the frequency with which stimulation of the central nervous system prevented several patients from continuing theophylline monoethanolamine suggested the use of a sedative, such as a short-acting barbiturate drug, when dosage requirement precluded sufficient reduction to overcome the undesirable reactions.

Second Series

To investigate these factors, the studies were repeated in a second series of forty-seven patients. The clinical procedure remained the same as in the first series, except that for most patients the initial dosage of theophylline monoethanolamine was 312 mg* in plastic containers of 37 ml capacity, called half-unit Clysmathane; these unlabeled half units were grossly indistinguishable from the full strength or standard units. Similarly packaged quarter strength or pediatric units (156 mg) were available for patients who had unusual degrees of intolerance for xanthine drugs. Patients experiencing undesirable reactions which might be controlled by mild sedation were given one or two capsules of pentobarbital sodium, 50 mg (¾ grains), with any of the preparations possessing sufficient clinical value to merit further trials. Since a great many patients of the second series, begun in September, 1959, would be suffering from ragweed pollinosis, the period of observation for each preparation was reduced to three or four days for those with seasonal distress, in order to complete the studies before symptoms subsided spontaneously.

Patients Not Completing the Second Series of Studies.—Four patients did not complete the second series of studies. In three, whose asthma was caused by ragweed pollen, symptoms abated after only two of the preparations were employed. Each of these three patients experienced better

*Average delivered dosage 250 mg.

relief with Clysmathane, one with half strength, than with aminophylline suppositories; in one patient local irritation caused by suppositories cleared during the Clysmathane trials. The fourth patient, with infectious asthma, needed full strength Clysmathane, although it nauseated slightly; she required hospitalization for vomiting after only one suppository. This patient refused other aminophylline preparations, and continued on Clysmathane, which she was able to reduce to half strength, with ¾ grain capsules of pentobarbital sodium taken orally.

TABLE IV. PREPARATIONS OF CHOICE REPORTED BY FORTY-THREE PATIENTS COMPLETING SECOND SERIES OF STUDIES

Preparations Preferred		Number of Patients
Preferring Clysmathane		
Full strength*	7	
Full strength with pentobarbital sodium	1	
Half strength**	24 (a, b)	
Half strength with pentobarbital sodium	5 (c)	37 (86%)
Preferring suppositories		3
Preferring equally Clysmathane and suppositories		2
Preferring crushed tablets as retention enemas		1
Total		43

(a) One patient nine years, one patient twelve years employed reduced dosage of other rectally administered drug preparations.
(b) In three patients proctitis from suppositories cleared during trials with half strength Clysmathane.
(c) In two patients proctitis from suppositories cleared during trials with half strength Clysmathane and pentobarbital sodium.
*500 mg average delivered dosage.
**250 mg average delivered dosage.

Patients Completing the Second Series of Studies.—Forty-three patients completed the second series of studies. Their preferences for the drug relieving them best with fewest or no side effects, in keeping with our criteria of evaluations, are shown in Table IV.

Restudied Patients.—Six patients who had preferred half strength Clysmathane in the first series were restudied and again arrived at their same decisions. One patient (1, Table II) who had discontinued the first series of studies after she was able to tolerate neither full strength Clysmathane nor enteric coated aminophylline tablets orally, on restudy could tolerate neither one-half nor one-fourth strength dosage of Clysmathane. One of the two patients who had preferred either half strength Clysmathane or suppositories, on restudy chose half strength Clysmathane with pentobarbital sodium; the other patient still had nausea with the half strength units, and changed her preference to suppositories. Another patient, who liked crushed tablet enemas and half strength Clysmathane equally, on restudy chose half strength Clysmathane with pentobarbital sodium. A patient who had preferred suppositories found insomnia and restlessness eliminated with half strength Clysmathane units, but he continued to prefer suppositories on the basis of convenience. The twelfth restudied patient was unable to retain even the half strength Clysmathane and continued in his preference for suppositories.

TABLE V.

	Theophylline Ethylenediamine (Aminophylline)						Theophylline Monoethanolamine (Clysmathane®)			
	Oral Tablets 200 mg.		Suppositories 500 mg.		Crushed Tablet Enemas 600 mg.*		Full Strength 625 mg.*		Half Strength 312 mg.**	
Number patients studied	87 (j)		88		88		57		47 (e, i)	
Patients reporting side effects	52	59%	52	59%	54	61%	41	71%	14	30%
Patients reporting no side effects	35		36		34 (f)		16		33	
Total number of side effects	69		103		91		68		13	
Upper gastro-intestinal irritation	50	74%	13	12%	16	18%	12	18%	2	
	1(b)				1(a)				1(a)	
Lower gastro-intestinal irritation	5	7%	80 (d, g)	77%	46 (c, h)	50%	31	46%	4	
(Aggravated Hemorrhoids)			3		3		3			
Central nervous irritation	8	12%	6	6%	21	23%	19	28%		
Restlessness	3		1		7		4		1(a)	
	2(a)									
Insomnia	1		1		9		13		3(a)	
			2(b)						1(b)	
Headache			2		5		1		1(a)	
Dizziness	2						1			
Miscellaneous										
Palpitation	4				3					
Tachycardia	1									
Generalized pruritis							1			
Urticaria					1		1			
"Weakness"			1							
Diuresis							1			

(a) Side effects controlled with pentobarbital sodium administered orally.
(b) Side effects not controlled with pentobarbital sodium administered orally.
(c) One patient used only 2 crushed tablets because of low tolerance for all xanthine drugs.
(d) Twelve-year-old patient used only ½ suppository (0.25 gm.).
(e) Twelve-year-old patient.
(f) Twelve-year-old patient used only 1½ crushed tablets (4½ gr.).
(g) Nine-year-old patient used only ½ suppository (0.25 gm.).
(h) Nine-year-old patient used only 1½ crushed tablets (4½ gr.).
(i) Nine-year-old patient. Pediatric unit Clysmathane® ineffective.
(j) Nine-year-old patient unable to swallow enteric coated tablets.
* Average delivered dosage 500 mg.
** Average delivered dosage 250 mg.

Patients Not Experiencing Relief from Any of the Preparations.—Four patients, all from the first series, could not arrive at definite conclusions concerning the merits of the drugs under study. One patient with asthmatic bronchitis and emphysema, who takes low maintenance dosage of corticosteroid drugs, experienced nausea, vomiting, or cramps from all the rectally administered products in the series, and could not take them long enough or in great enough dosage to permit relief. She had less nausea, but also only slight relief, from enteric coated aminophylline tablets orally; it is interesting that she takes Choledyl with benefit. Another patient with the same diagnosis, and who also relies on corticosteroid drugs, experienced only slight benefit, and either local irritation, or nausea and vomiting, from all the products used rectally; the enteric coated tablets of aminophylline did not relieve. On several occasions, but not invariably, this patient reported hives after taking Clysmathane. This patient also tolerates Choledyl, and resumed it at the termination of the study. The third and fourth patients, with permanent respiratory distress from chronic bronchitis and emphysema, did not experience relief from any of the medications.

Comparison of Side Effects from the Four Products.—In Table V are tabulated the side effects resulting from the use of each product employed in the study. In compiling these data, it was not always possible to distinguish severe from minor side effects, because many patients minimized such reactions if the product afforded relief. In the table, therefore, symptoms of intolerance are merely listed, without an indication of their degree. The most consistent side effects were referable to the gastro-intestinal tract. Nausea was the most frequent symptom of upper gastro-intestinal irritation, and was caused most often by the oral tablets. Anal irritation, which was noted most frequently following the use of suppositories, was often associated with symptoms of gastro-intestinal intolerance. A good many patients reported that after a variable time of fifteen minutes to an hour they expelled the rectal medications; this occurred most often with the aqueous preparations. We have included this as a symptom of lower gastro-intestinal irritation, although it does not necessarily represent "irritation," but merely the physiological action of expelling foreign matter from the rectum. Patients ordinarily did not object to this, because they absorbed the drug with good relief before expelling the aqueous enema vehicle. Stimulation of the central nervous system accounted for the third largest total number of unfavorable responses, and most often followed the use of the aqueous rectal medications. These side effects were significantly reduced in the Clysmathane series by the lower dosage, or were controlled entirely with pentobarbital sodium in all but one instance.

Convenience of Administration.—We were somewhat surprised that our patients did not distinguish more clearly between the various prepara-

tions in respect to convenience of administration. Fifty-six patients mentioned inconvenience, and all of these were concerned with the rectally administered preparations. Most inconvenience with use of suppositories resulted from the necessity of keeping one of the brands refrigerated; one patient was particularly emphatic on this point with the statement that suppositories were convenient at home, but very inconvenient away from home. The products were graded on inconvenience as follows:

Crushed Tablet Enemas	45 patients
Suppositories	9 patients
Clysmathane	2 patients
Oral Tablets	0 patients

Time for Relief from the Various Preparations.—We had anticipated that our patients could supply definite information regarding the time required for beginning relief, and for maximum relief, from the various theophylline preparations, but most of their answers on these points, especially the latter, were quite indefinite. There was general agreement that the two aqueous preparations employed rectally afforded relief more rapidly than did the others, and some patients felt that of these two, Clysmathane afforded relief faster, usually within ten to fifteen minutes. Suppositories were much less rapid in their action, and oral tablets were very slow, even in the few instances in which they afforded appreciable relief. Apparently, patients could not report more specifically on the time required for relief because they could not completely differentiate between this and degree of relief.

Clysmathane for Emergency Relief.—Frequently in the combined series of eighty-four patients who derived benefit from one or more of the xanthine preparations, the product of choice, when it was one of the rectally administered medications, could be used satisfactorily on a demand basis for relief of acute asthmatic attacks. Four patients employed full strength units of Clysmathane, and two used half strength units in this manner. Two other patients received intravenous injections of aminophylline and reacted with violent nausea before the injections were completed; they subsequently tolerated half strength Clysmathane with good relief. In three additional patients, Clysmathane was arbitrarily tried for acute attacks; these patients were not carried through studies with the other preparations. One patient had received epinephrine with benefit at 9 A.M. for acute allergic asthma; at noon he took a Tedral® tablet which did not relieve completely within one hour, whereupon at 1 P.M. he took one full strength dosage of Clysmathane, with relief persisting until the next morning. After another dose the following night, the attack cleared. Another patient with asthmatic bronchitis and left ventricular failure employed one Clysmathane unit every twelve hours with relief. The third patient, in status asthmaticus, had not improved with epinephrine, whereupon intravenous aminophylline was started but had to be discon-

tinued almost immediately because of severe nausea. After thirty minutes, Clysmathane in full strength was given with relief; this drug was continued every eight to twelve hours successfully.

DISCUSSION

In planning these studies, we realized that the amount of aminophylline contained in the 200 mg oral tablets could not be compared logically in clinical effectivness with the much larger amounts of xanthine drugs in each of the rectal preparations. However, we felt that more than 200 mg of aminophylline would not be tolerated in enteric coated tablets and our findings verified this assumption. Futhermore, the much greater tolerance of the lower gastro-intestinal tract for xanthine drugs would in itself be the main factor favoring rectal administration of the dosage necessary for relief. Our studies, then, essentially involved differentiation between the effectiveness of the three rectally administered preparations, in keeping with tolerance and convenience.

We can give no reason for the larger number of ano-rectal irritations caused in these studies by suppositories other than the fact that the xanthine drug remains in higher concentration for a longer period locally during the time the suppositories are melting. Further localization at the anal margin or on the perianal skin doubtless results from contact at insertion and this could be accentuated by a lubricating or an anal leakage effect after the suppositories melt. The relatively longer period required for clinical relief from suppositories reflects the time required for absorption.

Patient preference for Clysmathane, based largely, we think, on its rapidity of action,[10] was even more evident with the half strength, producing in turn fewer side effects in the second series. This is in keeping with unpublished experiments[9] in which Ridolfo found adequate blood levels following rectal administration of 250 mg of theophylline monoethanolamine. In the second series one patient requested a return to Clysmathane three times, two requested Clysmathane twice and three patients requested its re-use once, before proceeding with a study of the other preparations.

CONCLUSIONS

Theophylline monoethanolamine (Clysmathane® Fleet) in disposable units for rectal administration was found to be more effective for the symptomatic relief of bronchial asthma than theophylline ethylenediamine (aminophylline) employed rectally in suppositories or retention enemas, or as enteric coated tablets orally.

Employment of only one-half the dosage contained in the full strength unit of Clysmathane, and the simultaneous oral administration of a barbiturate drug in a few instances, materially reduced side effects without loss of therapeutic efficiency.

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ON THE STATE OF MEDICAL LITERATURE

Dismay in the doctor's study is also produced by the chaotic condition of the medical literature. The multiplication of it, the poor standards of it, the poor English that's written in it, the impossibility of keeping up with it, even with the digests of it. Just since 1940 this has become such a dreadful situation that I'm sure that many of us here could not possibly, in two weeks of sustained library study, adequately cover the literature of a single restricted topic. There might be any number of significant articles buried in all this trash which we would have missed. This is a monstrous system, which is self-reproducing. A new society gets started, let's call it the Society of Medical Semantics or something like that, and the first thing you know there is an annual meeting and a journal, and then there's a "call for papers," and then persons hastily get these papers together about three weeks before the next meeting, and finally the editor has a supply for the whole year. He can cull these papers, and he'll use his best talents of course and his best editorial work to see that he gets something a little less gruesome than usual—but you all know the result.—Sedgwick Mead, "Essay on the Art of the Practice of Medicine," *Kaiser Foundation* Medical Bulletin, 7:283 (Dec.) 1959.

THE OPSIPHYLACTIC TREATMENT OF RAGWEED POLLINOSIS BY MEANS OF A SINGLE ANNUAL INJECTION OF EMULSIFIED EXTRACT (X)

A Critical Study of 1064 Patients

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THE PRESENT paper describes the results of a study of 1,064 patients allergic to Ragweed pollen and treated during 1959 by means of one single injection ("one-shot") of emulsified pollen extract.

Two previously published papers of the present series of studies[1,2] discussed the treatment of, and the results obtained in, two rather small groups of thirty-eight and 685 patients, all allergic to Ragweed pollen, and treated by the same method for the respective pollen seasons of 1957 and 1958. The present communication extends these studies through the pollen season of 1959. Represented is a group of subjects sufficiently large to permit some statistical validation. The results of the earlier studies were not only confirmed but (despite the application of more rigid standards and a pollen season notorious for its severity) were better than could have been anticipated. Some of the implications involved in this particular study will, in future papers, be given full consideration. Only such will be mentioned in this paper as will help clarify some of the clinical aspects of the treatment of pollinosis by means of a single injection of emulsified extract.

The present paper will be limited to a discussion of, (1) the patient population distributed by age and sex, (2) the disorders treated and their duration, (3) the skin test reactions, (4) the levels and patterns of response of the so-called conjunctival tests, (5) the results of doses injected (a) in accordance with the degree of skin and ophthalmic reactions and (b) arbitrarily and regardless of either. Listed will be relationships, when present, between, (a) the date of the administration of the enapothetic* type of injection; (b) the dates when the symptoms, if any, first occurred and (c) the lack of relationship of symptoms to either the size of the dose administered, or the date of the injection. The few systemic reactions, their mildness and also again the lack of relationship between them and the patients' clinical allergy, test responses and doses of extract injected will be briefly described.

SYNOPSIS OF PRECEDING STUDIES

Of 685 patients similarly treated opsiphylactically* and enapothetically

*_Enapothetic_, Greek, deposit (from which, Latin—_apotheca_, storehouse, magazine). See also _apothesis_, Greek, a storing-up, and _apothetos_, Greek, stored up. All imply use. The word "repository" is derived from Latin, _repositorium_, a cabinet, a place in which objects or archives are stored, with the connotation that they are preserved and not for use, not changed, not depleted. In this and in future studies the word enapothetic will be used to describe any injection which is stored at the site of administration, regardless as to whether the type of emulsion results in near or distant future immunological effects.

for the Ragweed pollen season of 1958, fifty-six suffered from some hours of symptoms for a period of three contiguous or separated days. Fifty-seven others reported some slight discomfort. No matter how little discomfort there was, of any degree or however transient, it was in total present on only one or two days, during which it was usually limited to some minutes or hours. The two groups are further distinguished by the fact that the patients described in the first needed symptomatic medication, usually in excess of six tablets, often of an antihistaminic agent, but sometimes of an antispasmodic agent. Those more severely afflicted were treated with corticosteroid hormones, prescribed in some cases for seven to ten days. Some patients, once having suffered from any symptoms whatsoever, continued using the medicine until the end of the season, although it was not needed.[3] Post-seasonal and subsequent interim studies proved that almost all of the members of this group were affected by other seasonal and environmental allergens. It was thought that if these could be controlled either by elimination, when practical or feasible, or by treatment, when possible, then the overall results could be bettered, as shown either by the lessened number of patients with any symptoms whatsoever, or in the amount of discomfort the patients afflicted suffered. But, once more, attempts to quantitate qualitative states had to be abandoned. Although the subject will be discussed in a separate communication, some of the difficulties involved are described in a study concerned with the treatment of 564 patients allergic to the grass pollens of the New England area.[4]

CRITERIA OF PRESENT STUDY

It appeared that the two problems (namely, the quantitative and the qualitative) could be solved by the one means if the standards could be raised to a point which admitted no latitude in the interpretation of the results. This would also eliminate any unwitting bias on the part of the investigator, or, certainly, lessen it. For this third study of Ragweed pollinosis, therefore, any patient who suffered from typically allergic symptoms of any type, although fleetingly transient, and wholly subjective, for whatever reason, was arbitrarily classified as a failure. The application of such all-or-none types of criteria would exclude some of the fallacies inherent in the weighings of either "more-or-less" evaluations which, though quantitative in type, must qualitatively be interpreted. But

**Opsiphylactic,* from Greek, *opsios,* late, *opsiateros,* later, and *opsiatatos,* latest. See also *opsigonos,* late-born, *opsigamy,* marriage late in life, and *opsimathy,* educated late in life. *Phylax,* Greek, guard and *phylaxis,* watching or guarding. It is interesting that "prophylactic," from the Greek, *pro* and *phylassein,* also connotes to guard, but also to preserve, to prevent or to contribute to the prevention of, for example, disease. Strictly speaking, prophylactic treatment would prevent, not the symptoms of pollinosis, but the capacity, non-specifically, to become allergic. The word opsiphylactic has in the past and will in this and in future reports be used to define such types of injections as possess only delayed effects.

For example, the patients treated in April received opsiphylactic types of injections, whereas those treated with smaller quantities of emulsion and lower doses administered late in August and early in September received enapothetic treatment.

it soon became clear that the group of "failure patients" who knowingly had been exposed to inhalants or foods which, in the past had resulted in approximately equal responses when encountered extraseasonally, had to be omitted. In each case, however, the classification of the patient as a success or a failure in treatment was discussed with him, or, in the case of a child, with the parents, so that again, some Investigator Affect could be lessened, in that, although he sometimes differed with the patient or his parents, their decisions were accepted.

CONTESSERATION WITH CONCURRENT STUDIES

Because the opsiphylactic type of treatment of inhalant allergy is only one of a number of other types of studies of methods of treatment in progress, knowledge acquired from these could not be ignored, and could not be denied either to our allergic patients or to the physicians participating in the over-all project. Those of which the results are in preparation for publication or in press and which contribute to the significance of the present paper will briefly be synopsized, each in its place.

EXPERIMENTAL DESIGN

General Considerations.—Although Cuvier said, "The observer listens to nature; the experimenter questions and forces her to unveil herself," actually, at all times, both points of view were congruently present. As a result, as much knowledge overtook us as we overtook. Whenever such new knowledge proved itself to all practical purposes to be true, the general design of the experimental part of the studies was altered. It was difficult to separate observation from experiment, although many aspects of the study permitted this to be done. From observation alone, data could, as it were, passively be gathered, and although crude from the strict experimental point of view, might teach us how large numbers of patients would respond to a pattern of treatment quite different from that to which tradition had accustomed them. When faced with the choice of two types of treatment, it was, for example, quickly discovered that some, although few, of the patients, dependent in personality, actually enjoyed the frequent visits involved in traditional programs. But for ninety-eight patients of every hundred studied, the mention of the choice immediately made it apparent that almost all patients disliked the "work-ups" and the programs of injections with gradually increased doses of extracts. These interfere with many more activities than is first apparent.

For the experimental aspects of the study, it was necessary, actively and deliberately, to introduce sets of variables which, although admittedly not as yet proven to be important, might lead to the discovery of how best to take advantage of the enapothetic types of injection treatment. The patients, for example, were permitted to indulge themselves in any outdoor activity of their choice. The lesser exposure, which is so much a part of traditional programs of treatment, could not then be a major cause of

the improvement noted, if any. It was realized that other variables would be affected. Obviously, systemic reactions would be encountered in fewer numbers of patients with each successive group studied. But larger doses of extract could be administered to more clinically sensitive patients. How much larger the dose must be to play a significant part in the results is not as yet known, but that it plays some cannot categorically be denied.

Another variable affected by the improvement in the preparation of the emulsions was that concerned with "protecting" the patient. The safeguards to which emphasis had initially been given,[5] although necessary at that time, were no longer of great importance. Epinephrine was omitted. This, in itself, brought about an improvement in the degree of emulsification. It was obvious that the injection did not have to be given in divided doses. And from another study[6] it became clear that the ingestion of alcohol, at least for twenty-four to thirty-six hours after injection, increased the incidence of systemic reactions. A secondary safeguard was then instituted in that the adult patients were requested not to imbibe alcoholic beverages during the day of the injection. We similarly discovered that when a patient was allergic to a food which he could tolerate in minimal amounts extraseasonally, its ingestion within twenty-four to thirty-six hours after the injection was also followed, in a statistically significant number of patients, by urticaria. The interdiction of the foods which the patient knew or suspected to be a cause of symptoms again resulted in a lessened systemic reaction rate.

Preliminary returns from statistical studies now in progress, concerned with more than 12,000 injections of various emulsified extracts, proved that we could set up an experiment with so complex a design that there would be embraced up to thirty or more dimensions. But there would be little point in planning a study which would contain every possible combination and permutation of known variables, because these would actually encompass more than the computers available to us could handle.

EXPERIMENTAL DESIGN

Particular Considerations.—At the time of the preparation for press of the previous clinical studies, it was assumed that all readers would recall that the author had been associated since 1938 with the field of medical statistics.[7] It was then said, ". . . only by exact technique and by final mathematical evaluation by statistical methods can we ever feel that we know what we are talking about and have any likelihood of proving that we are right." To make certain that the conclusions reached by the overall studies would be statistically valid, consideration was given to a number of particular aspects in the treatment of pollinosis.

If a clinical study is to be at all acceptable, the investigator must make certain that the population treated is representative, in that there is no conscious or unconscious selection of patients. For example, to force the single annual injection type of treatment upon dependent patients

would, at least in them, make the lack of continuous supervision a source of dissatisfaction. In the absence of insight the patient might exaggerate any symptoms which did occur so that he might have an apparently valid reason to return to a program of frequent visits to the physician. Obversely, had non-dependent patients alone been chosen, they might also have suffered from minor degrees of discomfort, but would, as part of their personalities, have not reported them.

The patients, therefore, were taken at random as they were referred by colleagues; came for treatment on the basis of recommendations of relatives or friends; or were themselves physicians or members of physicians' families. Some reported for treatment because they had failed to respond to traditional measures employed for sufficiently long periods of time, or had suffered systemic reactions either many in number or severe and perilous if not life-threatening, or for the simple reason that they wanted to change because they were not content with other methods of treatment. Some of the dependent types of patients were given a single injection of emulsified extract, and permitted frequent return for office visits, evaluation studies, and if asthmatic, for pulmonary function tests. Others were given the same single injection of emulsified extract, but returned at intervals of once every three or four weeks for injections of placebos, usually physiological saline, to which was added 0.05 ml of epinephrine, 1:1000.

The variables of sex, of age, of disorder (type and duration), and of previous treatment, if any (successful or unsuccessful), were allowed to take care of themselves. It might have happened that because of local conditions, a low pollen count would have resulted in a short run of successfully treated patients. But fortunately, the geographical distribution of the patients was not in our hands, and it was soon apparent that local variations in pollen count could not affect the results, because of the fact that the patients were resident in approximately forty states, Mexico and Canada. There were those who had changed their residence or had been transferred because of occupations. Those who knew that they were to return East during the respective pollen seasons often took treatment only so that they would be free of symptoms during the summer and autumn.

Excepting for physicians and members of their families, no patient was accepted for the enapothetic type of treatment unless three or more consecutive seasons of pollinosis had been experienced. The previously published tables and those in the present communication indicate how many patients have suffered from fifteen to forty or more consecutive seasons of symptoms. But this was not considered sufficiently critical, and no one who reported a period of affliction of fewer than four weeks during any one season was permitted to take an injection, excluding the obvious exceptions which had to be made for those patients who were allergic to several successively pollinating species of trees.

No patient was given either opsiphylactic or enapothetic treatment unless a skin test response with wheals and pseudopodia could be elicited by solutions of pollen extract of concentrations of whatever is represented by 2000 P.N.U./ml or less. Those patients who suffered from what appeared to be typical pollinosis, but in whom such positive skin test responses could only be elicited with stronger solutions of extract, were given no injections until they had proved by one or more seasons of observation that they were sufficiently sensitive to the pollen in question to merit such treatment by the opsiphylactic type of injection.

As a matter of fact, the patients described in this report represent (by any standards and especially those of the visiting and participating and the referring physicians, as well), the greatest reactive, the poorest responsive, the most recalcitrant, and in several hundred cases the notorious failures of other physicians' practices and those of the public clinics. Many of the patients had not responded either to decades of multiple injection treatment or to corticosteroid hormones, although the first had been given perennially, and the second prescribed for seasonal use. A number of the patients had been hospitalized on one or more occasions during each of the previous pollen seasons.

As regards the date of administration of the injection, we had little choice. Had every patient been given his own way, almost all would have requested appointments during June, at the time when schools were closed and before summer vacations began. When the patients left the choice to us, we, when practical, randomized the date of the injection by arranging to treat them on the basis of the alphabetical sequence of their names, as random a method as can be imagined. It is possible that all those of Scottish or Irish derivation might have been seen on approximately the same dates. But, except for such bunching around the thirteenth and fifteenth letters of the alphabet, sufficient randomization was obtained by such simple means as to be beyond cavil. Additional randomization was assured by permitting any patient who was not satisfied with the appointment sent him to choose an injection date between the limits of May 1 and August 1. Time was made available from August 15 to September 3 for those patients who wished treatment only when certain of symptoms. They could in every case be sure on the basis of past histories that when such symptoms were present, they would usually last until mid-October or well into early November. New patients were treated on the days on which they reported for studies.

In clinical practice, however, experimental designs cannot slavishly be followed, in that patient demands may govern the actions of the physician. Discussed in their proper place will be the sixty-two patients we had to include as in transition from the multiple visit to the single visit type of treatment. Those who took such treatment for only a month or two could well be considered as placebo patients or as controls, although they are tabulated as in transition.

What of placebo-reactors? In chronic disorders, such as pollinosis present for many years, these do not in reality exist in numbers which need concern us. One might well wonder what happens to the patient who, for example, has suffered from attacks of seasonal allergic coryza for ten consecutive years, and having taken treatment for eight with no acceptable relief, responds with complete absence of symptoms to one injection of emulsified pollen extract. When on the basis of so good a result the patient is told not to return for treatment until symptoms recur, and the relief is observed to last for two or three years but noted as recurring during the fourth, then the effect, if placebo in type, is certainly longer than any previously recorded.

As far as we can discover, there is no published study in the field of immunology involving the use of placebos in which the placebo has been omitted entirely for the second or third year after the first injection to make certain that the "protection" afforded by the initial injection was not in itself a placebo. It is obvious that in a patient who presents no symptoms during the second year of exposure, treatment with a placebo cannot of itself prove retroactively that he had not needed the injection of pollen extract for the first year. And a patient who receives an injection of true pollen extract for the second year may also enjoy a similar long-lasting protection. The fact that in him no symptoms occur does not prove that the second injection was not a placebo. A number of our patients who have responded to neither of two successive placebos became symptom-free following an injection of emulsified extract. But from this we cannot argue that the practice of medicine is like a baseball game, and that it takes three placebos to strike a patient out.

The complexities of the problems involved are not usually appreciated. Available to us are the possibilities of changes in the ingredients of the emulsions as regards these alone. Of such emulsions we now possess five. Work in progress with substitutes for mineral oil will undoubtedly give us at least ten preparations, each characterized by differing properties. Whatever type of emulsion is used, we know that its rate of absorption can also be modified by choice of the site of injection. It is equally obvious that the number of units of extract present in any given quantity of emulsion can be varied. Should we wish to omit the possibility that the patients' immunological responses may differ, all things being equal, and that the amount of patient exposure may vary, although no part of the experiment is otherwise permitted to vary, nevertheless, we are concerned with variations in clinical sensitivity, date of administration, total dose injected, quantity of emulsion used, type of emulsion being studied, and site of injection chosen. When we add the variables of either untreated patients or successfully or unsuccessfully treated patients in direct transition, or else with one or two seasons of symptoms bridging the transition, it becomes clear that there are many more variables than at first appear significant.

To quote from a paper in preparation,[8] "It is obvious from every table so far published that Means, Modes, Medians, Frequency Polygons and Histograms add nothing to the significance of the study. No purpose is served by calculating the average dose. There is no such entity as an average patient who reacts in an average number of minutes with an average skin test response of average size to a solution of average strength, and who, on the basis of such a vague standard of hypersensitivity receives an average dose to which he responds with an average clinical result because of an average exposure during an average season, during which he suffers from an average number of average stresses and equally average strains. Should he indeed be so average, then why is he in reality so different?" In this regard a remark by Julian Huxley is particularly apt. He says, ". . . one of the great needs of our time is to discover means of coping with the problems of quantity and values: after all, our most important experiences are qualitative and when everything has been reduced to mathematics something essential has evaporated from reality. Until we can do this we will be in danger of what may be called the 'nothing-but' fallacy—of assuming that the higher can be explained in terms of the lower from which it happens to have, in part, originated."

We must remember that the same and a number of additional criticisms can be leveled at traditional methods of treatment. We are not in agreement as to how an extract should be prepared and what should be the standards of measurement of potency or allergenicity or potential of protection. We cannot measure the degree of sensitivity. We do not know the ideal date on which to initiate treatment, and there is no unanimity of opinion as to the amount of first dose; the number of injections to be given; the length of time treatment should continue and the total amount of the last dose. In fact, we possess no means of measuring the patient's response to any or all of the injections excepting as he reports amelioration of states for which no descriptive terms exist and for which there are again no methods of measurement. Otherwise, we do quite well.

The same statistical studies show that the only similarities between the opsiphylactic and the progressive dosage forms of treatment are that, for both, the physician must use pollen extract, and that such extract must be injected. But by no stretch of the imagination can the obviously new type of treatment be termed a modification of the old. This statement can be made because the subjects of comparison were studied by means of sequential analysis of the double dichotomy type (that is, an analysis of the results of the observations as either good or bad, and, again, the results of the test as a decision between two methods of treatment).

Although the statistics we have collected do not furnish what is mistakenly called "mathematic proof," they will be published as a separate report, although in the long run, they cannot be used to replace lack of clinical judgment or to fortify it excepting by means of such conclusions as may have been reached on those flimsy foundations of probability which

cannot be applied, excepting peripherally, to clinical studies of this type.

It is interesting to note that there is a point at which theoretical quibbling cannot obscure the fact that the patients treated opsiphylactically are somehow different from those who have, in many cases, been equally successfully treated by traditional methods. Not only do the patients themselves learn this, but no visiting physician has failed, intuitively as it were, to note, without prompting, that something very different has taken place in these patients, and that this something, whatever it may be, cannot be expressed in terms of tidy mathematical formulae.

THE EXTRACT

Three types of pollen extract are in use for separate investigations. The preparation of the one used for the present study has been described;[9] the second and third will be reported upon in a separate communication concerned with the duration of the clinical effects of a single annual injection, as observed for two or more successive pollen seasons.

THE EMULSION

For the purposes of the present study all of the patients received the 1:9:10 (Arlacel A: Drakeol 6VR: Extract) type of emulsion previously reported upon *(op. cit.)*. The fact is that other types of emulsions are now in the process of evaluation, as prepared with or without potentiating agents of both the water-soluble and oil-soluble types. These also will be the subject of separate reports, as used in the treatment of other populations of patients. It should be emphasized that the emulsion as described for the treatment of the patients studied in the present report is no longer in use, because of changes involving (1) the ingredients and substitutes for them, (2) the quantities of each used, (3) the process of emulsification, and, (4) the increased stability of the new types of properly prepared emulsions. It has also been shown that the extract remains potent at body temperatures (in the body itself) for the duration of the absorption period. Also, the ultimate disposition of the ingredients of the several types of emulsified extract has been determined. The emulsion used for the present study will, however, adequately serve the purposes of corroborative investigations.

THE PATIENT POPULATION

The population studied for the present paper consisted of approximately 1,000 patients given one injection of emulsified pollen extract. For comparative purposes, we once again used a second population of approximately 500 patients, who received traditional types of treatment. The first was permitted only one degree of freedom, and the second more than ten degrees. Of the first population, only 144 of 1,064 reported symptoms, and of the second, almost 200.

For simplification of comparison, the first table has purposely been made similar to those previously used in the other studies of this series. The ages of the patients represented by the population treated for 1959 varied

TABLE I. THE PATIENT POPULATION DISTRIBUTED ACCORDING TO AGE AND SEX

Years	3-5	6-10	11-20	21-30	31-40	41-50	51-60	61-70	71-77	Total
Males	14	78	174	89	109	88	42	23	8	625
Females	4	30	101	70	96	81	39	16	2	439
Total	18	108	275	159	205	169	81	39	10	1064

from three to seventy-seven years. The oldest patient treated in 1958 was permitted to go without further treatment. It will be noted that the number of patients ten years of age and under increased from fifty-three (in 1958) to 126 for 1959. Obviously, some of the younger patients have suffered only from one to two years of symptoms. These had been so well authenticated that for them the criteria could be less rigid. For the series of patients treated in 1958, seven varied in age from seventy to eighty. For 1959, the group increased to ten, who varied in age from seventy-one to seventy-seven years.

THE DISORDERS TREATED AND THEIR DURATION

The second table needs no textual comment. Comparatively speaking, the number of patients who suffered from Bronchial Asthma increased from 156 in 1958 to 211 in 1959, whereas the number of those who

TABLE II. THE NUMBER OF PATIENTS DISTRIBUTED ACCORDING TO DISORDER AND DURATION

Years	3-10	11-20	21-30	31-40	41-50	51 or More	Total
Number of patients with bronchial asthma	116	52	23	7	12	1	211
Number of patients with allergic coryza	238	129	53	25	8	3	456
Number of patients with bronchial asthma and allergic coryza*	147	135	73	25	5	1	386
Number of patients with other disorders	6	3	2	0	0	0	11
Total	507	319	151	57	25	5	1064

*In cases in which both disorders were present, only the duration of the disorder which appeared at an earlier date is listed.

suffered from Hay Fever grew from 253 to 456. The patients whose illness could best be described as total respiratory tract pollinosis increased from 269 to 386 in number. Many of these patients did not necessarily suffer from both disorders during all of each pollen season. When both had been suffered in sequence or concurrently, the duration of the earliest appearing manifestation of pollinosis is listed. The number of miscellaneous disorders attributed to allergy to pollen is not worth tabulating,

although it should be noted that of these patients, there were eleven, as compared to seven in last year's series.

THE CRITERIA OF POLLINOSIS

For none of the studies so far reported was any patient given any injection treatment on the basis only of conjunctival and intracutaneous tests and in the absence of proven symptoms. In other words, no patient received so-called "prophylactic" treatment, because it was thought that a large positive skin test reaction in a patient otherwise allergic might presage symptoms of pollinosis, which could perhaps be prevented by antecedent injections of pollen extract. Although for the previous studies the patients who did not react by skin test, but were reactive by other proofs of pollinosis, were not permitted treatment, there were included in the present study sixteen who had been under observation and who were authentically allergic but reactive intracutaneously only to stronger solutions of extract than those customarily used (2000 P.N.U./ml). Seven patients were reactive to actual Ragweed pollen, but were skin test negative. The percentage they represent of the total number of patients treated does not exceed that previously reported upon by others, and including them in the study does not significantly distort the results obtained.

THE CONJUNCTIVAL TESTS

In our own previous reports, it had been stated that the dose of extract injected has, in many cases, been based on the degree of conjunctival response. This system of treatment had to be followed because at the time there were available the results of a few studies which concerned what was later discovered to reflect experience with small numbers of selected patients. Our own experimental studies soon proved that this type of test did not indicate the clinical degree of sensitivity. As noted elsewhere *(op. cit.)*, some of our observations had been made by Feinman as long ago as 1926. Not only does the conjunctival test not indicate the degree of clinical sensitivity, but it does not help to determine the dose to be administered, either for reasons of safety or for maximum protective effect. The results of our own critical evaluation of this type of test, if such it may be termed, forced us to abandon it for a number of reasons which will be separately reported upon.[10]

In brief, on the basis of more than five thousand sets of conjunctival tests done on more than 2,000 pollen-sensitive patients, before and after the usual symptom season, and pre-seasonally, before the next injection, it was discovered that there were at least forty-two consistent patterns of response,* and that these and six others for which examples were not sought were mathematically in accordance with all the possible combinations and permutations of the design inherent in the study. In order to make certain that there was no bias, all the possible types of responses

*See footnote, page 642.

were listed in advance. The patients' statistical cards as used for tabulation purposes were arranged alphabetically, and each type of response was noted under the appropriate heading until twenty-five examples had been collected. There were not enough unsuccessfully treated patients for

TABLE III-A. THE NUMBER OF PATIENTS DISTRIBUTED ACCORDING TO CONJUNCTIVAL REACTIVITY

Testing Solutions in P.N.U./ml	5	10	20	40	80	150	300	600	Sub-Total
Number of patients	4	13	33	94	107	107	71	50	479

TABLE III-B.

Testing Solutions in P.N.U./ml	1200	2500	5000	10,000	15,000	20,000	Total
Number of patients	48	40	30	23	14	29	663

In sixty-seven patients who were allergic to grass pollen and who reported for treatment during the season for the pollen of which they had received no injection, the ophthalmic test would have furnished no useful information. In 334 patients, there were no conjunctival symptoms and for the test-concentrations used, no ophthalmic response. The levels of concentration needed to elicit a positive response in the remaining 663 patients are listed.

us to be able to collect twenty-five examples of each of the patterns of response for these. This is, however, a matter of little importance, because the chosen number, namely twenty-five, is not important in this particular frame of reference. From the point of view of sequential analysis, ten or fifteen examples would have been more than enough, and in any case the studies can be continued until any arbitrary number of examples has been collected. The frequency curves for the various types of responses are also not important. They only tell us how probable it is that a patient will fit into one curve or another. But again, however improbable the event, should it affect any individual patient, then for him there is a 1:1 relationship, and after all we deal with patients in particular, and not in general.

The criteria for inclusion in the study were: (a) a proven clinical allergy to the pollen as evidenced by actual observation, (b) a recent history of symptoms which had occurred on days and during hours when other patients were similarly afflicted; (c) a clinical pattern of symptoms as bolstered by controlled exposure, or again, if needed, insufflation of the pollen itself, or, in asthmatic patients, the use of nebulized extracts, and (d) positive skin test reactions by dilute solutions of the same pollen extract used either for the pressure-puncture or the intracutaneous method

*For the reader interested in the forty-two patterns, they are ascertained by adding to the twelve responses (to be discussed) six responses each for patients either successfully treated for one year and the next, or successfully for the first year but with symptoms during the next, or vice versa, or those unsuccessfully treated for two consecutive years, or those with non-specific positive tests, but otherwise allergic. (As for example, the patient with proven Ragweed pollinosis, who for twenty consecutive years demonstrates a positive grass pollen test, but never suffers any symptoms.)

of testing. It was understood that the conjunctival tests could not be done in infants, in the blind, and in patients at the time affected by allergic or non-allergic conjunctival disorders.

The one pollen extract was used throughout these studies, and for all the types of tests. In patients in whom the conjunctival symptoms could objectively be corroborated, the responses in those who had either successfully or unsuccessfully been treated could be listed under six headings for each, a total of twelve. The test was either negative initially and became positive, or was negative initially and remained unchanged after treatment. An initially positive test might become negative, or else a positive test might not change in that it could be elicited with one dilution more or less. A positive test might become more positive, that is, be capable of being elicited by more dilute solutions of extracts, or else become less positive as proved by the necessity for using more concentrated extracts. The change was not considered significant unless at least three and usually four or more dilutions were needed. To use one example, a patient whose eye test could be elicited with 5 P.N.U./ml, and then after treatment, only with a dilution of 160 P.N.U./ml, was labeled as being less sensitive. If in another patient the test, initially elicited with the 160 P.N.U./ml solution, could be evoked with 5 P.N.U./ml after treatment, the patient was listed as more sensitive. But this type of change represented the acceptable minimum. There were many examples of patients who went from a negative test at the 10,000 P.N.U./ml level to a positive test with 5 P.N.U./ml, although treated with complete success.

The same twelve types of responses were elicited for successfully and unsuccessfully treated patients for whom there never had been any record of conjunctival symptoms, but in whom there were other proven symptoms or signs of pollinosis, of the upper, but often only of the lower, respiratory tract.

The study was extended so that patients, otherwise allergic, but nonspecifically reactive conjunctivally to Ragweed pollen, could be included. In these no autoumnal symptoms of any type had ever been experienced, and therefore no injection treatment had ever been given. Examples of the six differences in types of responses (of course only when the positive reaction was present) could also be elicited. And the same six types of patterns of response were also observed in Ragweed pollen sensitive patients who were under observation, and who therefore received no injection treatment whatsoever. We did not test normal, non-allergic patients. Although the incidence might be small, there is no reason to believe that examples of each type of reaction could not be uncovered, as postulated from the fact that these patients might not as yet have suffered from pollinosis and at the clinical level.

It was quickly apparent that it was not possible to determine from the patient response to any particular dilution or concentration of extract what the same patient's degree of clinical sensitivity might be. Because

of changes encountered, it was soon discovered by retrospective analysis that the test, whether it remained the same or changed in either direction, had not indicated the results to be expected of any postulated exposure to actual pollen. It was not changed by the amount of pollen extract injected. Although there were only twenty-five systemic reactions, as will be discussed, nevertheless, in this small number of patients in this particular study the test did not indicate the patient's tolerance of any particular dose of standardized emulsified extract.

For whatever they are worth, Tables III-A and III-B list the conjunctival test responses as based on successive dilutions which during the course of the studies were rounded off to the nearer whole number, as convenient for laboratory purposes. A sufficient number of tests proved that the test response was so coarse that it made no difference whether the dilution used was 150 or 160 P.N.U./ml, or to take another example, 300 or 320 P.N.U./ml.

For the 663 patients so tested for the present study, the tables only list the level at which injection of the conjunctiva of one eye was elicited, as corroborated by the use of the next higher concentration instilled into the other eye. These tables are included only for the purposes of record. The data presented, for reasons to be given, warrant no valid conclusion.

In a previous communication *(op. cit.)*, it was stated that these present studies were in progress, and that groups of patients would be treated with doses of extract based on the degree of the conjunctival responses elicited. It was said, "Those (patients) reactive at the 5, 10, or 20 P.N.U./ml level will receive only 500 P.N.U." It was also stated that patients reactive at the 40 P.N.U. level would receive 1000 P.N.U. doses and sequentially 1500 P.N.U. for the 80 P.N.U. response, 2000 for 160 and 2500 for the 320 P.N.U. positive test.

In general accordance with this experimental design, of fifty patients who reacted ophthalmically at the 5, 10 and 20 P.N.U./ml levels, only eleven received 500 P.N.U. (compare Tables III-A, III-B, and V), and ninety-four patients conjunctivally reactive to 40 P.N.U. received 1000 P.N.U. By coincidence alone, 107 patients reacted to 80 and another 107 to 150 P.N.U. Of these, only fifty-seven received doses of 1500 P.N.U. and sixty-two, 2000 P.N.U. Whereas only seventy-one showed positive tests to 300 P.N.U., 151 received 2500 P.N.U./ml doses. Nineteen patients took injections of 3000 P.N.U., one, 3500 P.N.U., and six, 4000 P.N.U. All the others of these groups received larger doses with neither local nor systemic reactions.

There were thirty-nine patients who were not treated in accordance with the lower doses suggested by the conjunctival test response, because they had either previously taken, with safety, higher doses, or else, were to be changed from a high dose of unemulsified extract to an equal dose of emulsified extract. The ophthalmic response, if at all significant in any patient, certainly could not be applied to these thirty-nine. Because the

factor of safety exhibited by such injections of unemulsified and emulsified extracts for reasonable amounts of such pollen solutions varies from 10 to 1000 multiples, there was no reason to reduce the dose to be injected.

It might be concluded from the data presented in the tables that the patients listed as responding to dilute solutions used for conjunctival tests were those of the greater or greatest clinical sensitivity. In them, either less pollen in quantity, or else less exposure in time might have resulted in symptoms, or else, following a given amount of exposure to equal amounts of pollen, the patients might have responded with more intense suffering. Interviews proved some to be afflicted mildly and only for the four weeks represented by the last ten days of August and the first twenty days of September, with limits of four or five days, usually more and not less, and others apparently equally responsive by such tests, recorded symptoms which began during the second and third weeks in August and ended by the middle of October or later. As will be presented in another study, the more sensitive patient needs not smaller, but larger doses.

At first glance it would also appear that twice as many patients, ninety-seven, given smaller doses based on so shifting a foundation of measurement of sensitivity, did not do as well as the forty-seven of 614 who were treated with higher doses (compare Tables V and IX). But although one group is twice the size of the other, the difference is not statistically significant and could have occurred by chance, given the sizes of the two groups and the same level of confidence.

Although the systemic reactions encountered will be discussed separately, their lack of relationship to the conjunctival test response will more easily be comprehended if this aspect of the study is at this point reviewed. Of the twenty-five systemic reactions experienced, twenty followed doses of less than 3000 P.N.U. (see Table XI). All of these patients were conjunctivally reactive. The other five reactions occurred after the injection of doses of 5000, 6000, or 10,000 P.N.U. But the twenty occurred in patients in whom the level of conjunctival reactivity supposedly informed us as to what the "safe dose" might be. In each of these the dose injected was less than that recommended. The five other systemic reactions occurred in patients not conjunctivally responsive, but given arbitrarily chosen doses, the choice being made at random. We do not know whether the same mild systemic reactions might not have occurred following the injections of smaller doses. We do not know that such systemic reactions can occur in patients who do not respond, as we had mistakenly reported (on the basis of the few systemic reactions previously encountered), to conjunctival test levels of 320 P.N.U./ml or less. Every previously reported incident had occurred in patients of such apparently consistent conjunctival level responses. Exceptions at both ends of the curve of reaction of susceptibility vs. conjunctival test responses were soon observed. In other words, patients who do not respond conjunctivally can respond systemically, and other patients previously untreated, but with

conjunctival responses to as little as 5 P.N.U./ml, can apparently take with safety a dose of 10,000 P.N.U. No significant relationship existed between the positive conjunctival test response at any level and the absence of conjunctival symptoms or their presence in any degree. In addition, it has not been ascertained whether the test truly reflects the presence, and not the degree, of allergy of the upper respiratory tract, or is apparently a mirror of the degree of clinical symptoms, or else is non-specifically present as regards the eyes themselves.

In an attempt to corroborate these conclusions, a second study of 500 patients allergic to other pollens was undertaken. In them no conjunctival tests were done. Three dose levels were used, namely, 2500, 5000 and 10,000 P.N.U., either given at random to previously untreated patients, or else the lowest of the three doses to those with apparently great clinical sensitivity, with the intermediate dose injected to those of more moderate clinical symptoms, and the upper dose arbitrarily given to every patient who had previously had treatment. Any patient in the group who had previously been treated with emulsified extract and had reacted, however slightly or severely, received double the dose which was supposedly followed by and therefore the cause of a systemic reaction. In all, five mild reactions, limited to local, forearm or upper arm urticaria occurred in three patients, and generalized scattered urticae in two more. The one patient whose reaction followed the ingestion of a large amount of alcohol immediately after the injection needed epinephrine. A second patient who planned to travel some distance after the injection was also given epinephrine although it was not needed. The three other patients responded to antihistaminic agents.

Obviously, then, the conjunctival reaction neither indicates the clinical sensitivity nor the maximum dose which can be given, nor the dose which can be injected with safety. The continued studies also suggest that, contrary to our own earlier reports, it cannot in general be used to presage the possibility of a systemic reaction.

THE SKIN TEST RESPONSES

A separate study concerned with the skin test responses of a series of 5000 patients tested serially by clinical methods over a period of five to twenty years is in preparation. It is possible to relate the results of this study of allergic patients in general to the 1064 patients allergic to Ragweed pollen and who were given particular study.

It has been postulated that the patient's degree of clinical sensitivity may be related to the skin test response, as elicited by tests, by either the scratch or pressure-puncture or intracutaneous methods, using serial dilutions of standardized extract. It has been thought that not only did a larger response to a more dilute solution indicate that the patient was not only clinically but immunologically more "allergic," but that the presence of so large a response to so dilute a solution might help determine the

first dose to be administered, the successive increases to be followed, and as well, indicate the probability that systemic reactions might occur.

In brief, it was possible to classify the patients into at least six large groups according to their skin test responses at 10,000, 20,000 and 40,000 P.N.U./ml used for percutaneous and 100, 1000 and 2000 P.N.U./ml, as similarly used for intracutaneous test purposes. In no patient did the degree of response to any strength of extract consistently reflect the level of clinical symptoms. Allowing for dermatographia at the one end, and ichthyosis at the other, the same number of examples could be found for the validity of the test response as for an equal lack of validity.

There were patients, for example, clinically allergic to a higher degree, who reacted to the pressure-puncture test of the highest dilution used. But each such consistently reactive patient could be paired with another who showed the same skin test response, but whose symptoms were mild indeed. The obverse reaction pattern could equally often be uncovered. In addition, in at least 500 patients, the test level remained unchanged regardless as to whether successive seasons of exposure were associated with mild or moderate or severe symptoms. Fluctuations in clinical response were not paralleled by the skin test reactions as titrated to an exact end point.

In both successfully and unsuccessfully treated patients, regardless whether such success or failure followed the injection of large amounts of either unemulsified or emulsified extracts, the skin test response, when present again, either remained the same or else varied, going in either direction when elicited by the intermediate strengths of a series of concentrations, as for example, from a 10,000 P.N.U./ml scratch test positive response to a 2000 P.N.U./ml intracutaneous negative response, or vice versa. In few patients indeed, in whom a skin test could not initially be elicited, could the positive type of reaction later be evoked. In many more patients, however, there were years during which the skin test response could be elicited before and after treatment and the test response varied. This pattern occurred regardless of whether the patients were clinically completely, or partially, or not at all relieved as a result of their injection treatment. In patients treated only symptomatically, and in those given placebo injections, similar changes or no changes in skin test reactivity were noted. In patients who were enjoying spontaneous remissions, following the menopause, for example, the skin test level of reaction might not change, or again, from any intermediate point, go in the direction of either increased or decreased reactivity to extracts of greater or lesser concentration. The direction of the change did not predict the patients' future clinical courses. Of course, in no skin test reactive patient was it possible, from any change in skin test response, antecedently to predict a successful or unsuccessful result following any type of injection.

In addition there were the non-specific positive tests seen in "normals" who had never shown any stigmata of any type of allergy, and also the equally non-specific positive skin test reactions, as repeatedly confirmed

annually for periods of up to twenty years in either a tree or grass pollen sensitive patient. In these, for two decades no symptoms had ever been caused by Ragweed pollen. (With more exact measurements of slight degree of response to Ragweed pollen, it might be possible to show that these patients were allergic to the pollen in question but, at sub-clinical

TABLE IV. THE NUMBER OF PATIENTS DISTRIBUTED ACCORDING TO SKIN TEST REACTIVITY

Testing Solutions in P.N.U./ml	P.P.P.*	+100	+1000	+2000	+4000	+10,000	Total
Number of patients	347	145	115	434	12	4	1057

*P.P.P. refers to positive responses to pressure puncture (scratch test).

The total number of patients does not equal 1064 because for seven patients, there was no positive response. In those cases in which two or more responses to serial tests were elicited, only the largest response to the greatest dilution is listed.

levels, which caused no objective or subjective states of discomfort, and by present measures no objective changes.) And, in any case, twenty years is not a sufficiently long period of observation, in that some of these patients may eventually demonstrate true Ragweed pollen allergy. There were, obversely, patients who by all known criteria were allergic to the Ragweed pollen itself, and in whom no skin test reactions could be elicited with extracts so concentrated that these approached the level of non-specific irritative strengths. They, however, numbered approximately 1-2 per cent of the total population studied. The successful clinical result achieved in such patients by means of injections of Ragweed pollen extract only in part proves that they were allergic to the pollen, inasmuch as there are too few to permit the measurement of non-specific responses, or those placebo in nature.

It is therefore once again concluded that, although in a previously untreated patient the skin test response might conceivably represent something, it certainly ceases to represent anything of significance after the very first injection in that it does not change, or else, after several injections, may change regardless of the patient's partial or complete "protection." It is certainly not significant when it is more easily elicited with a solution more dilute in a patient who as a result, or as a sequence of injection treatment of any type, is completely well. Should he conceal from a second physician the fact that he has safely taken, and with a successful result, a dose, for example, of 10,000 P.N.U., then the intracutaneous test response elicited by the second physician at the 100 P.N.U./ml level would signify to him that the dose he must administer should be one protein nitrogen unit, that is 0.1 ml of a 10 P.N.U./ml solution, a manifest absurdity.

The fourth table is here included only as a matter of record. The data represent a classification of patients according to the levels of their skin test reactivity, with only the largest response to the greatest dilution being listed. The patients who responded to the pressure-puncture types of tests reacted to solutions represented either by 40,000 or 50,000 P.N.U./ml. No useful purpose would be served in grouping the patients

according to the varying responses to differing dilutions of solutions used for pressure-puncture test purposes, because of the large number of variables, which will be made the subject of a separate communication.

Mention has been made of the number of patients treated in accordance with the positive conjunctival test responses. In these patients, the degree of skin test sensitivity was completely ignored. Although in the greater number of patients the test in general agreed, there were of course those with large responses to dilute solutions by skin test, and with no conjunctival responses whatsoever. The opposite picture was less frequently seen. In every patient who reacted conjunctivally there was always some skin test response, although in some patients it could only be elicited with concentrated solutions. In the patients who needed either a 4000 P.N.U./ml or a 10,000 P.N.U./ml solution to elicit a skin test response, no conjunctival reactivity could be evoked although solutions of a concentration of 20,000 P.N.U./ml were used. The seven patients who did not react by skin test were also conjunctivally non-reactive.

TABLE V. THE DOSES OF EMULSIFIED EXTRACT ADMINISTERED AND THE NUMBER OF PATIENTS TREATED WITH EACH

Dose (P.N.U.)	500	1000	1500	2000	2500	3000	3500	4000	5000	6000	7500	8000	10,000	Total
Number of patients	11	143	57	62	151	19	1	6	137	10	205	1	261	1064

The number of patients listed in the column to the left of the double line were treated according to the level of the conjunctival response. Of these 450, ninety-seven (see Table IX) suffered symptoms, as compared to forty-seven of 614 treated with arbitrary doses given at random.

THE DOSES ADMINISTERED

In an attempt to lessen the complexity of the treatment of pollinosis, and with the conviction that there was a zone of dose levels within which a difference of say, 2500 P.N.U./ml, was not significant, 137 patients received doses of 5000 P.N.U./ml, with 205 given 7500 P.N.U./ml, and 261, 10,000 P.N.U. Attempts to treat with intermediate doses were abandoned because they were not practical, and therefore, only ten patients received 6000 P.N.U./ml, and one patient, 8000 P.N.U./ml. In two other separate studies, each comprising more than 500 patients, the dose represented by 7500 P.N.U./ml was eliminated, because the difference in response was discovered not to be significant.

Comparisons of the Tables V and IX show that approximately the same number of patients with symptoms were seen in each of the groups of patients given the three doses, namely, 5000, 7500 and 10,000 P.N.U./ml. Twelve of 137, fifteen of 205 and nineteen of 261 respectively reported difficulties. It would appear that the larger doses probably brought about a more successful result, but again it must be recalled that a 10,000 P.N.U./ml dose was given either to patients who had previously been treated by multiple-visit or single-visit programs, or else were considered to be less allergic by clinical history. It is not easy to divest one's self of the results of previous training. When a patient responds little

to the intracutaneous injection of a concentrated pollen extract, or presents a history of symptoms limited to the dates associated with the higher pollen counts, it is impossible to get one's self not to give him a sizable dose of pollen extract. When two of the 261 patients suffered from systemic reactions, attention was focussed on the technique of administration; but when six systemic reactions were recorded for patients who received doses of 1000 P.N.U./ml, it was concluded that the dose administered was in excess of the patient's pollen tolerance (whatever "tolerance" may signify). It was quickly discovered that the patients who had reacted systemically to the smaller dose were not necessarily more allergic to the Ragweed pollen, but more allergic to more allergens, clinically or by skin test. The systemic reaction may have been due to their levels of heightened general response, and not to the injection itself.

Indirect evidence that this might be true was demonstrated by the patients who took, without systemic reactions, much larger doses of the same extract, although in a better emulsion form, administered two and sometimes three years after the first had been taken. It was at first thought that there was either residual protection, or else that the greater emulsification had resulted in greater safety. Although neither possibility can be ignored, nevertheless it must be noted that these same patients had learned, as a result of their studies and continued observation, to eliminate from their environments or their diets inhalants or food to which they were clinically or sub-clinically allergic, in that only greater amounts of exposure or ingestion caused objective symptoms. In some cases, pets had been eliminated, and in others treatment for other inhalant sensitivity had been initiated and successfully accomplished.

The total number of reactive patients was too few for us to be able to prove by any direct means that this conclusion was valid. But, there was a means of discovering indirectly whether it could, with some confidence, be tenable. A search of the statistical cards of all the patients treated showed that patients could be paired on the basis of equal skin and eye test responses, and, as far as it could be ascertained, histories of equal degrees of clinical allergy to the same but not to other pollens. When these same patients were given doses of up to twenty multiples of those which had been followed by systemic reactions, there resulted in them neither local nor general effects. When the studies showed that for every reacting patient ten or more so distinguished could be found, then the future treatment of multiply allergic patients was based on this tentative conclusion, and the systemic reaction rate was lowered by two thirds. As the emulsion is improved, the rate becomes progressively lower, both in over-all percentage and, as well, for each successive group studied and treated. * In other words, it is the patient's allergic state and not the

*In another study in preparation, in which more than 1,000 Ragweed-sensitive patients were treated with another type of emulsion, transient, mild urticaria occurred in only five.

dose which, within reasonable limits, is responsible for the systemic reaction. On this basis an unbroken series of emulsified extract injections numbering in excess of 6,000 (of a total of 12,000) has been administered with not one systemic reaction having been experienced by any patient no matter how "allergic" clinically or by eye or skin tests.

In any case, the foregoing discussion is only of historical interest in that we now possess a new and hitherto undescribed method of determining the ideal dose for any patient, regardless of the degree of his skin or eye test response. This will be the subject of a separate communication.

THE TRANSITION PATIENTS

Included in the group of Ragweed pollen sensitive patients studied for the 1958 season were 196 (of the total 685) who had never before taken any injection of Ragweed pollen extract of any type. In the present study, 421 (of 1064) had similarly never before received an injection.

TABLE VI. TRANSITION PATIENTS
Distribution According to the Number of Months Since Injections of Unemulsified Extract Had Been Administered.

Number of Months	Less Than One Month	1	2	3	4	5	6	7	8	9	10	11	12	More Than One Year	Transition Patients Total
Number of patients	5	5	6	6	5	4	4	5	5	0	2	3	2	10	62

The relationships are obvious. The second population is approximately twice as great. Arithmetical doubling of the number of the previously treated patients of the first study (196 x 2) makes it clear that 392 of 1370 (29 per cent) is not as great as 421 of 1064 (39 per cent).

In none of these 421 patients could the response be of the anamnestic type. In their treatment, no other factors were involved than either the injection of extract, or else the largest number of placebo reactors ever recorded.

Of the population treated for 1958, some 489 had taken injections of pollen extract at some time or other. The number was reduced to sixty-two of our own transition patients for the study of 1959. The number of such "transition patients" is smaller than at first appears. Of the sixty-two patients, eleven, of their own volition, began treatment by the multiple-visit type of program. Of their own choice, and within two months, the change-over was made. They certainly received little enough injection treatment with the unemulsified extract given them. Although it is not likely, the minute amount of extract involved might have "conditioned" them for the enapothetic type of injection. It is known that this can occur with virus vaccines and some drugs. Separately reported upon will be an extension of such studies to treatment with pollen extracts. A simple technique enables us to locate such identified antibodies as may result from each of the two types of injections.

Ten of the sixty-two transition patients had experienced symptoms

because no injections of unemulsified extract had been administered for more than one year. Table VI also lists seven patients of whom two had taken treatment until May, three until June and two others until July of 1958. All had previously been treated elsewhere on the basis of sixteen to twenty-four injections of unemulsified extract administered preseasonally. None had measurably been helped. Only forty-five patients can truly therefore be termed "transition patients." They represent less than 5 per cent of the total number treated. It can then no longer be said that the results noted are due to the anamnestic type of response.

THE DATES OF INJECTIONS OF EMULSIFIED EXTRACT

The period of treatment for 1959 spanned the weeks between the middle of April and the end of August. The injections were usually administered on Tuesday, Wednesday, and Thursday of each week.

TABLE VII. THE DISTRIBUTION OF PATIENTS ACCORDING TO THE DATES THE INJECTIONS OF EMULSIFIED EXTRACT WERE ADMINISTERED

Month	April	May	June	July	August	September	Total
Number of patients	2	281	500	141	125	15	1064

The two patients who received their injections of emulsified extract during the second week in April were going abroad, to return during the Ragweed pollen season.

The patients listed as treated in September include those whose symptoms were present, but whose period of affliction usually extended into late October. They received symptomatic treatment for three to seven days.

When the two patients who could not report for treatment excepting during April are excluded, then it is clear from the present study, 281 patients received single annual injections of emulsified extract during the twelve working days of May, 500 during the thirteen working days of June, 141 patients during the fifteen working days of July, and the last 125 during the twelve working days of August. Fifteen patients, the subjects of a special study, were treated during the first days of September. All had previously recorded having been afflicted until middle or late October, or when allergic to house dust, as late as November. All were obviously ill at the time of treatment. All received several days of symptomatic treatment, which in the past had been followed by partial relief and had been needed for six to eight weeks.

From the same seventh table it is obvious that approximately half the total number of patients (500 of 1064) were treated during the month of June.

DATE OF SYMPTOMS

The date on which patients report having had their first symptoms does not represent a simple datum. From Table VIII it will be noted that thirty-five patients reported difficulty beginning on August third and subsequently for three or more days up to and including the fifteenth. A pollen field survey proved the Ragweeds to be pollinating abundantly on

Sunday, August second. The first patients with symptoms were interviewed and examined on August fourth. During this period of time, a type of Ragweed, which as far as we can discover has never previously been described, was the source of the pollen. It will be the subject of a report to be published elsewhere.

TABLE VIII. DISTRIBUTION OF PATIENTS WITH SYMPTOMS ACCORDING TO DATE SYMPTOMS FIRST OCCURRED

Dates	August		September		Total
	3-16	17-31	1-14	15-30	
Number of patients	35	67	26	16	144

One of the forty-two patients listed as noting symptoms after September first had received an injection on September third. None of the fourteen other patients who received their injections after their symptoms had been present for two or more weeks reported any difficulties after a short period of symptomatic treatment.

The subsequent group of afflicted patients began to notice symptoms from Monday, August seventeenth, through Monday, the thirty-first, by which date 102 patients in all (almost 10 per cent of the total treated) had reported their awareness of the pollen season. The days of the week are mentioned because in so many of the patients the clinical reactions to pollen afflicted successive groups over the days represented by each of the successive weekends, when exposure is usually greater. Those who drove to and from work noticed some late-afternoon-and-evening rather than awakening-in-the-morning symptoms. Only twenty-six more patients became aware of symptoms during the following two weeks of Ragweed pollination, with sixteen others reporting the initiation of symptoms between September fiteenth and thirtieth, presumably as belated or late season responders or else because of increased exposure to house dust or to molds.

The cut-off date for the review of data was at first set as of December 31, 1959, so that the patients who had not needed injection treatment for house dust or molds or who had not taken advantage of the availability of injections of emulsified influenza viruses and poliomyelitis vaccines, or of yearly re-evaluation studies, could, if subject to tree pollinosis, be interviewed when they returned for treatment. The cut-off date was later extended until April first so that the patients who were also allergic to grass pollen could then be subjected either to a first interview when not previously reporting or to second and third interviews to test their recollections of the past pollen season's symptoms. All were requested to repeat their evaluations of their treatment. There were no cases of paramnesia, in that so few varied in the words actually used that the generally held opinion that the patients forget their past sufferings because these are dimmed by memory and therefore are not trustworthy was proven to be invalid. There are some patients who do minimize their discomfort after the event. There are as many who maximize the amount

of affliction they have undergone. The number, in either case, was not great. They all remember, only too well, what it was like before they were treated by the single injection of emulsified extract. This aspect of future clinical reports will therefore be ignored. The typical "good patient" may accept the traditional type of treatment program, but he subconsciously objects to it, and no matter how friendly he may be, he is deeply resentful of the restrictions it imposes upon him.

The later cut-off date enabled us to unearth several patients who had not reported their symptoms at the time these had occurred. But, their excuses were that the discomforts were often too minimal to necessitate medical treatment. Several patients (fewer than six) reported more severe difficulties. A detailed interview proved the symptoms of each to have occurred before and after the period of Ragweed pollinosis or to have been the result in every such case of advenient causes as, for example, exposure to smoke, to fumes, to fresh paint or to animal danders. One patient, allergic as well to grass pollen for which no treatment had been received, reported severe symptoms lasting up to the third week in August but not thereafter. He might have been reacting to exposure to both types of pollen for only one of which an injection (Ragweed) had been given. The tables were not worth changing so that he might be included.

It was interesting to note that two groups of patients could be paired. Those multiply allergic (it will be recalled), more often reacted systemically, although the incidence was small. These same patients more often did not achieve a perfect result. It cannot from this be concluded that they should not have been treated enapothetically. When antecedently hyposensitized by means of unemulsified extract injected in small doses progressively increased in amount, they reported having suffered from many systemic reactions and these all of them more severe in depth and longer in time. They could not in any case ever be treated with all of the allergens which caused their symptoms, if only because these are either too many in number or when used do not result in good clinical responses (for example, feather dander), or else again, are in their own right, toxic as are kapok and cottonseed. Exposure to these can be diminished when they cannot completely be eliminated from the patients' domestic environments. Unfortunately such patients do visit other people's houses and are, as well, sometimes visited by non-allergic friends who could contaminate the patient's homes. In these same patients when such events could be subjected to detailed study, the resulting symptoms, it was discovered, could last as long as ten to fifteen days. They rarely affected the patient for more than twenty-four to forty-eight hours when he was exposed away from home. Indirect proof that this was true could be obtained when the same patients purchased or acquired pets. They needed medical treatment within a day or two of exposure, but removal of the animal or bird was not followed by immediate relief but instead the

symptoms persisted mildly or subclinically as measured in asthmatic patients, by diminished vital capacity, for periods of ten or more days and sometimes as long as a month.

The patients listed in the last column of Tables VII and X deserve textual comment. These fifteen subjects were referred for treatment because of moderate to severe symptoms which had been present since early or middle August. They had usually been afflicted by pollen until the middle of October or later, and expected, on the basis of their own past histories, an additional five or more weeks of symptoms. Each was informed that the enapothetic type of treatment might have no effect or, if any, then clinical relief of some degree could be expected within a period of seven to ten days, although it might be as early as five days or be delayed for two or three weeks. In both cases it would coincide with decreasing amounts of ambient pollen. There was also the possibility that the symptomatic treatment prescribed for the first three to seven, and in several patients, for ten days, could of itself be enough to protect them for the remainder of the season. In addition, each was informed that the relief of symptoms might be due to suggestion alone, unwittingly or unconsciously the result of the patient's attitude, expectant of relief. But in any case, in every patient the antihistaminic or antispasmodic agents prescribed were to be taken routinely for three to seven days in accordance with the ensuing weather as indicated by the long range reports. Obviously, when a storm center was expected to pass north or south, and cyclone or anticyclone winds were responsible for more or less pollen, this was reflected in the length of time medicine was needed. The patients could thereafter take their medication as needed.

Regardless of the degree of the skin or the eye test responses, each patient received in a single dose, administered intramuscularly, exactly 1000 P.N.U. of Ragweed pollen extract in a total quantity of 1.0 ml of emulsion. Only one patient suffered from symptoms, and these were milder than those experienced during preceding years. He needed some medical treatment intermittently throughout the pollen season, but declared himself pleased with the result. But, of all of the other patients treated, there were forty-one (therefore giving the total of forty-two noted in the last two columns of Table VIII) who, having received their injections at what were considered to be the ideal dates and with either the use of large or small doses of pollen extract, reported having been conscious of discomfort caused by pollen after September first.

THE RELATION OF SYMPTOMS TO DOSE

Mention has been made of the structure of the two concomitant studies done. Did emulsification sufficiently potentiate the number of units injected to the extent that a smaller number of such units might have been injected with equally good results? Until the results of the third study (for which 1500 patients will be chosen) are available, it should not be

concluded that these same either partially protected or unprotected patients, given any number of units of any magnitude of dose, would not have had some difficulty. As noted, the numbers of patients respectively treated, namely, 450 and 614, were not sufficiently large to warrant conclusions of any validity.

TABLE IX. APPARENT RELATION OF SYMPTOMS TO DOSE LEVEL

Dose in P.N.U.	500	1000	1500	2000	2500	3000	4000	Sub-Total	5000	6000	7500	10,000	Sub-Total	Total
Number of patients	3	34	16	16	25	2	1	97	12	1	15	19	47	144

It is our current belief (based perhaps on training of which we cannot completely divest ourselves, but to which we must hold fast until it is modified by more evidence) that those patients who are given larger doses do better than those given the smaller doses and that both groups of patients do better than do the subjects who have been treated with placebos in whom it has constantly been demonstrated that, in time, symptoms always occur and in every one almost without exception. Indirect proof of the validity of this tentative conclusion can be drawn from those previous unpublished studies concerned with the patients treated on the basis of frequently administered microscopically small doses of extract. Despite initial enthusiasm for this fad, so many patients were so severely afflicted that this program of treatment was quickly abandoned not only by us, but almost universally.

Table IX is self-explanatory. It over-simplifies the possible relationships of any reported symptoms to the amount of extract injected. As previously stated, the numbers treated are not sufficiently large to warrant a generalization of merit.

TABLE X. APPARENT RELATION OF SYMPTOMS TO DATE OF ADMINISTRATION OF INJECTION

Dates	April		May		June		July		August		September		Total
	1-15	16-30	1-15	16-31	1-15	16-30	1-15	16-31	1-15	16-31	1-3		
Number treated	2		281		500		141		125		15		1064
Number with symptoms			13	24	28	33	9	12	10	14	1		144

Of the 144 patients listed, fifty-five were proven to be allergic to the predominant molds, and seventy-two to house dust. In seventeen, the tests to these two allergens were negative or not done because they were deemed unnecessary.

THE RELATION OF SYMPTOMS TO DATE OF INJECTION

Because of the long-lasting effects of the opsiphylactic types of injections which, in some patients, extend up to and beyond three years, a separate but concurrent study has been initiated in order to discover how early and also how late it was possible to administer the emulsified extracts, and what types of emulsion were needed for the more delayed of one, and the less delayed effects of the other.

It is clear from Table X that of 281 patients treated during the month of May, a total of thirty-seven reported symptoms. They are only apparently (when compared on a month-to-month basis) few. Of the 500 patients treated during June, sixty-one were affected. The twenty-one of 141 and twenty-four of 125 who respectively received their injections during July and August are remarkably comparable in numbers. The well-being of the patients treated during early September may have been the result of one or more of the several favorable factors previously noted.

The thirty-seven of 281 (May) can legitimately be compared by simple arithmetical doubling to become a hypothetical seventy-four of an equally hypothetical 562. The difference between this number and the true sixty-one of 500 (June) is so small that the numbers affected can be considered to be approximately equal. The application of more complex statistical methods suggests that the difference is not at all significant.

A review of the subjects' histories proved fifty-five of 144 to be mold sensitive. Their symptoms occurred during the last days at the end of a spell of rainy weather with recovery during the subsequent fair weather, which was of course characterized by much more ambient as compared to flotation pollen. Of the same 144, seventy-two patients were allergic to house dust, but had received no treatment for it. In them the symptoms occurred only during September and with exposure to the presence of both pollen and dust. In only seventeen of the 144 patients was there no evidence of allergic responses to other allergens, seasonal or environmental, inhalant or food, although these may have similarly played some part, however little, in causing the symptoms noted.

But these symptoms were in any case so mild that no additional treatment would have been recommended because it is always suggested and to every patient who has successfully responded to treatment that he be content with the minimal number of injections administered at the most infrequent intervals possible so that the least amount of injected extract, which will keep him symptom-free for the longest possible period of time, can be discovered. He need not face the future with anxiety because should any symptoms occur, the injection which had not been administered at the usual date could then be given him, although he might need several days or, at the most, a week or ten days of concomitant medical treatment for such discomfort, which often disappears within six to eight hours.

The injections of placebos are, therefore, no longer needed to validate the results of treatment, because the patients in any case only report for additional injections of extract when objective symptoms have undeniably recurred and are present. This type of evaluation of any method of treatment for a chronic and recurrent disorder permits placebo effects (if any) to wear off. When periods of freedom of symptoms do last for long periods of time the patient need not be subjected to either valid or else to false placebo types of controls. We have fulfilled our medical obligation to him for as long a period as he stays well and periodical evaluation

studies prove no deterioration in his health, other than that caused by the process of aging. Should the good effects not be placebo in nature, then allowance has been made for the possibility of a natural remission. This may also be the result of the injection, or of a spontaneous lessened allergic irritability, or of equally efficacious lessened exposure, or because of any number of other reasons at present beyond our methods of detection, or proof of presence of any type of immune antibody. We have no explanations for this phenomenon and no hypotheses. It is just as well that we admit our lack of knowledge as to why it occurs.

SYSTEMIC REACTIONS

Although all of the systemic reactions encountered during the injection of more than 12,000 doses of emulsified extract will be the subject of a separate report which will be concerned with this one aspect of treatment by means of injections of emulsified and unemulsified extracts, brief

TABLE XI. DOSES RECEIVED BY PATIENTS WHO SUFFERED SYSTEMIC (BY DEFINITION) REACTIONS

Dose (in P.N.U.)	1000	1500	2000	2500	3000	5000	6000	10,000	Total
Number of patients	6	1	8	4	1	2	1	2	25

mention should at this time be made of some of the characteristics of such special responses. Those which are supposedly caused by treatment of the enapothetic type differ from the anaphylactoid type of constitutional reaction which follows upon injection of non-emulsified extracts. The patients, in almost all cases, have never before been treated, and in fact have not ever been skin tested. They frequently but not invariably react to the pressure-puncture type of test when extracts in high dilutions are applied to the epidermis. They are usually clinically miserable from the first to the last days of the season and most important are not only, as noted, more allergic to pollen but also more allergic to more allergens for which treatment has not at the time of the injection been initiated.

In the beginning, the reactions sometimes occurred during the very administration of the emulsified extract, especially when it was administered in the mistaken belief that the "divided doses" technique was the safer of the two procedures. The reactions were, in many cases, caused by the damaged tissue subsequent upon the use of the supposed exact same site. As noted, this type of reaction was not seen in a series of approximately 5,000 injections given in accordance with a technique which resulted from a special study concerned with the administration of any allergen by hypodermic means.

When most mild, the reaction which the patients most frequently described was a sudden sensation of a general flushing of the skin. No other organ was affected. This flushing occurred only once and was noted,

in earlier studies, from two to four hours following the injection. It might last for thirty to ninety seconds and vanish before medication could be taken. The duration might extend to twenty or thirty minutes, but, by this time, the antihistaminic agent could be exerting its pharmacologic effect. Even in some previously untreated patients the reaction lasted no longer. In one patient it was associated with a "tight feeling" in the throat and with transient dysphagia.

In other patients the conjunctivae and the lids alone were affected, the first becoming injected and the second angioneurotically swollen. The antihistaminic agents usually appeared to prevent extension, at least local in type, but the swelling might persist for several hours and in two of ten patients was barely visible during the morning of the following day. In each the injection had been administered during the late afternoon.

The patients subject to urticaria would react with hives, although the injected pollen itself usually caused seasonal upper, lower and total respiratory tract symptoms. Antihistaminic agents were effective by mouth or by intramuscular injection with diminution noticed in fifteen to sixty minutes and when following intravenous injection in five to ten minutes.

In none of the reactive patients has there been noted any swelling of the site of the injection at the time of the reaction, although such evidence of local response may occur, but usually within a period of six to twelve hours with the more primitive types of emulsions and with present-day emulsions in twenty-four to thirty-six hours after their administration.

Of the twenty-five patients included in the present study and labeled as reacting systemically, ten were allergic to grass pollen. Their injections were administered during the months of the grass pollen season. Because a systemic reaction is so defined as to include any symptom whatsoever, ocular, nasal or pulmonary, it is possible that the reports of such symptoms, especially when they had similarly been experienced either before the injection of Ragweed pollen extract or on occasions during the weeks following the injection, but not after the cessation of grass pollination, were not in every patient directly due to any effect of the injection itself. All of the so-called systemic reactions of which we can be certain occurred, as noted, within six to ten hours after the injection had been given. They differed in all respects from the anaphylactoid types of general reactions which have been described as caused by the injection of unemulsified extract. Not one patient given an injection of emulsified pollen extract has ever responded with the shock-like syndrome usually termed a systemic reaction. Not one has needed so-called emergency treatment. Not one has been hospitalized. None has been frightened away from future treatment excepting for a Japanese patient, with whom no communication in English was possible. The patients are instructed to take a tablet of d-chlorpheniramine maleate, 6 mg (Polaramine Repetabs, Schering) and then another in four hours, should a flush or pruritus occur. In some cases, the tablets are prescribed prophylac-

tically to be taken at bedtime and three times during the following day. Some patients, although so instructed, prefer not to take the antihistaminic agents. They have proved to themselves, and to us, that such protection is indeed not necessary.

There has been some criticism of the so-called systemic reactions recorded (chiefly by others) as following upon injection of poorly or partially emulsified extract. Two important factors must be recalled if this aspect of the opsiphylactic treatment is to be regarded in its proper perspective. First, the reaction rate is a crude datum, in that we do not know how many reactions would have been experienced by these same patients when given the same top dose or total dose by means of traditional methods of treatment. But the second and better measure of the safety of the treatment with emulsified extracts can be determined from the past histories of these same patients. One of the population here described reported having suffered from twenty-four systemic reactions, some so severe as to require hospitalization, although the unemulsified extract had been injected by an allergist of note. The record of a second patient, a physician's secretary, shows that she had reacted systemically on at least thirty separate occasions, although every injection was preceded by the ingestion of antihistaminic drugs, and each dose was mixed with enough epinephrine to make its effects noticeable. Some of the doses were not increased until the previous amount had been given for at least five successive weeks before the injection of the next higher dose of the schedule was administered. Obviously, when with previous treatment, two patients of the group of 1,064 had suffered twice as many systemic reactions as were reported by all of the 1,064 patients, no statistician is needed to measure the probabilities involved as regards the safety of the one method of treatment as compared to the other.

There are at least six factors involved, and with attention to these, almost no reactions occur, no matter what method of treatment is used. Chiefly, when the technique of injecting extract is itself poor, then reactions will, of course, occur but less often subsequent to the injection of the smaller doses. The fewer systemic reactions noted with traditional types of preparations are only apparently few in number, because the physician hardly ever increases the dose. The patient is often informed that his subsequent symptoms have occurred because he is too "sensitive" to take with safety a dose which would confer protection. The inconsistencies and puzzling features of systemic reactions are not inherent in the patient but in the techniques of the physician. In other words, as regards extracts, dose increases, sites of injection and methods of administration, it is more often the operator than the operation.

MISCELLANEOUS FEATURES

It must be emphasized that what we have learned from the twelve or more studies so far completed (although what has been reported repre-

sents a great advance over traditional methods of treatment) does not constitute a platform on which the allergist can firmly stand and therefrom easily treat all allergic disorders. The successive studies (of which there are four in press and more than twenty in preparation) must be looked upon instead as efficient spring-boards. In this regard the word "efficient" connotes two of its several meanings, (1) possessing the capacity to produce the desired results and, (2) effective with a minimum of waste effort. Both significances apply to the enapothetic type of treatment. But what has been described is only to be taken as a *saltus empiricus,* or preferably as an *instauratio magna* (the moving forward of a delimiting palisade), and not as a final or definitive basis for treatment in the far but rather only in the immediate future.

The decade it took to review forty to fifty years of the treatment of pollinosis by traditional methods[11] precipitated us, at first, into the more proximal parameters involving only the injection treatment of inhalant-caused allergic disorders. It soon became clear that the one variable, namely injections of extract, was only an arbitrarily ill-defined constant and that it was obviously modified by a number of other intercepting and qualifying variables, the functions of which also, in some cases, needed definition and in others, elucidation and solution. There is then more to the treatment of pollinosis than the injection of progressively increased quantities of extract.

The full significance of the present paper can, therefore, only clearly be comprehended when it is studied in relationship to the other investigations being done. It appears in print only as a matter of record and as a grace-note of historical interest. As a result of anaplesis (that is, the ontogenetic acquisition of new knowledge as derived from the experience here described) and of ancillary research work soon to appear in print, it must be stated that almost all of the techniques here described have been superseded by improved methods for the treatment of those allergic disorders which regularly follow exposure to seasonal or environmental types of allergens.

In any case, to quote Carlyle, "Our grand business is not to see what lies dimly at a distance, but to do what lies clearly at hand."

SUMMARY

A small group of 1,064 patients allergic to Ragweed pollen, as determined by history, examination, conjunctival and both percutaneous and intracutaneous tests, and as indicated, by instillation, insufflation and nebulization procedures, were each treated by means of a single injection of emulsified Ragweed pollen extract. The patients varied in age from three to seventy-seven years. Except for eleven patients who suffered from extra-respiratory system allergy, 386 were afflicted with total respiratory tract pollinosis, and 456 others with upper and 211 with lower respiratory tract symptoms.

The duration of the disorder(s) varied from three to fifty or more years.

Of the 1,064 patients, 450 patients were treated with doses based on conjunctival and skin test responses, and the other 614 (except for a few) patients were treated arbitrarily with doses of 5000, 7500 and 10,000 P.N.U. given at random. The differences, taking the population as a whole, were not significant, although twice as many (97 ± 33 as compared to 47 ± 33) reported symptoms. As regards each group taken separately, there is equally no difference (97 ± 22 as compared to 47 ± 25). The sixty-two transition patients all did well. Their numbers are too few to warrant any valid conclusions.

There were again no apparent clear relationships between the dates of the injections and the doses of extract administered and the dates of onset, the severity, or the durations of the symptoms, if any, reported. The results, however, have been bettered for each of nine consecutive studies. Although approximately 13 per cent of the patients reported some discomfort and these are listed as failures, no matter what the cause of the degree, yet of these patients fewer than 2 per cent were truly reactive only to the Ragweed pollen. No other method of treatment achieves such quick results of so great degree and with as high a factor of safety.

But this is not enough! Studies in progress are concerned with better techniques of the preparation of both the extracts and the emulsions. As needed, either more quickly produced or else longer lasting effects can be obtained. The use of water-soluble and oil-soluble potentiating agents enable us to reach yet higher clinical levels of protection. These will be the subjects of separate reports now in press or in preparation.

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POLLINOSIS IN NORTHERN ISRAEL

Clinical Report

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POLLEN SURVEYS in Israel have been limited to the major towns and their immediate environments. Kessler[1] surveyed airborne pollen in Tel Aviv and its surroundings, Guttman[2] and Parag, Feinbrun and Tass,[5] studied the problem in Jerusalem. No pollen surveys are available for the northern part of this country.

During 1955-1957, we made a clinical and pollen survey of the northern parts of Israel. This study is based on the results of intracutaneous and scratch tests on allergic patients. The correlation of these results with atmospheric pollen studies and a pollen calendar will be reported, when such data become available.

The northern part of Israel is distinguished from other parts of the country by its developed agriculture, rich vegetation and forestry. The total surface of the area to be described is 4,331,000 dunam (1 acre=4 dunam). Out of this, the cultivated area is 1,621,000 dunam and planted forests 150,000 dunam, a total of 1,771,000 dunam, or 40.9 per cent of the area. The rest (59.1 per cent) consists of forest reserves, natural pasture, mountains, uncultivated land and built up area. It is to be noted that the proportions change as a result of the rapid development of the country. We find an abundance of *Pinus, Cupressus, Ceratonia siliqua, Olea europeaea, Pistacia, Eucalyptus, Schinus, Quercus,* and others.

Except for *Olea,* most of this vegetation is of little allergenic importance. Olive trees, growing densely in this part of the country, are known to be primarily entomophilous, becoming anemophilous in the later stage of anthesis. In addition to the plants of the various botanical groups mentioned above, the grasses, such as *Cynodon dactylon, Dactylis glomerata, Lolium, Sorghum halepense, Poa pratensis and Poa annua,* play an important part.

Along the shore of the Mediterranean, we found the well known allergenic plants of *Artemisia* growing in the sandy soil. Here we meet the *Artemisia monosperma* 7, which contributes to some cases of pollinosis among the population of this part of the country. In the surrounding areas of Acre, we found *Salicornia herbacea L.* and *Salicornia fruticosa L.* from the *Chenopodiaceae,* anemophilous plants which cover great spaces in this territory. Many representatives of the *Chenopodiaceae,* as Salsola and others, were also found. No Ambrosia or related species were detected in this part of the country.

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SUBJECTS AND METHODS

Material surveyed in this report consists of 421 patients with pollinosis, who have attended the Allergy Clinic of the Workers' Sick Fund (Kupat Holim) in Haifa. This area is inhabited by 543,000 people. Since this is

TABLE I. POLLINOSIS IN ISRAEL
(1955-1957)

Age Group	Number of Cases	Per Cent
1-10 years	39	9.2%
11-20 years	85	20.3%
from 21 years	297	70.5%
Sex		
Male	218	51.7%
Female	203	48.3%
Total number of cases	421	100 %

the only allergy clinic in northern Israel, the clinical material is fairly representative. All the patients studied have been submitted to the routine diagnostic intracutaneous and scratch testing with pollen extracts and bacterial vaccines. Patients were checked for immediate reactions following diagnostic procedures with pollen extracts; whereas, both immediate and delayed reactions were checked when bacterial vaccines were used.

RESULTS

As seen in Table I, the cases of pollinosis are equally distributed between the sexes. The patients were divided into three age groups. The highest incidence of pollinosis (70.5 per cent) was found in the age group of twenty-one years of age and older. The teen-age group (eleven to twenty) comprised 20.3 per cent of the cases, while the youngest age group consisted of 9.2 per cent of all cases.

Grasses were found to be the etiologic factor in 56.5 per cent of cases (Table II). It is noteworthy that 14 per cent of the patients were positive to Olea alone, while the combined reactions to Olea and several grasses reached 20.4 per cent.

Among the population of the Kibbutzim and settlements along Haifa Bay and Acre, we have found sixteen patients (3.8 per cent) who reacted to Artemisia alone. Of the same population, the patients who reacted to Artemisia and grasses, and to Artemisia and Olea numbered thirty-eight, which is 9 per cent of the total. It would thus appear, that the three most important etiological factors in pollinosis in this part of the country are: (1) Grasses, (2) Olea and (3) Artemisia.

On the basis of the clinical observations, as well as of the cutaneous reactions, it was found that in 161 cases, or 38 per cent of the patients, pollen allergy was accompanied by bacterial allergy. It is understood that in this group we relied on clinical symptoms, as well as on the bacteriological diag-

nosis, before testing with vaccine. With all cases of sinusitis, tonsilitis, rhinitis and bronchitis giving positive bacteriological diagnosis, we employed both the routine tests for pollinosis and vaccine tests.

In only 149 of the patients (35.6 per cent) did we establish a history of familial allergy.

TABLE II. POSITIVE INTRACUTANEOUS AND SCRATCH TESTS

Etiological Factors	Number of Cases	Per Cent
Gramineae	238	56.5%
Olea	59	14.0%
Olea and gramineae	86	20.4%
Artemisia	16	3.8%
Artemisia and gramineae	14	3.3%
Olea and artemisia	8	1.9%

CONCLUSIONS

1. It is of interest to note the relative importance of Olea europaea pollen as a cause of hay fever in a great percentage of our cases. This fact had not been fully appreciated previously. The Artemisia cases are also important, especially among the population living in the coastal area of this part of the country.

2. This emphasizes the fact that a close co-operation between allergist and botanist is essential in any study aimed at a rational understanding of the etiology of allergies.

3. The establishment of a pollen calendar and the study of atmospheric pollen are basic prerequisites in the clinical diagnosis and treatment of pollinosis.

SUMMARY

1. A clinical study was made on 421 patients with pollinosis, drawn from all parts of northern Israel. All patients were submitted to intracutaneous and scratch tests as well as to bacterial vaccine tests.

2. The most frequent allergens were found in grasses, Olea and Artemisia.

3. Numerous trees and plants found in this part of the country were also tested for antigenicity, but failed to give reactions, and could be excluded as antigenic.

4. In 38 per cent of pollinosis cases a bacterial component was also established.

5. A family history of allergy was elicited in only 35 per cent of the cases reported.

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NEW PROGRAM REGARDING NEW DRUGS

A program for the reporting of unusual or adverse reactions to drugs was announced recently by the Food and Drug Administration. It is to be conducted initially with a limited number of hospitals selected to represent a cross section of medical specialties. Where necessary, contracts may be negotiated with the hospitals (or individual physicians designated by them) providing for reimbursement. As the program develops, it is planned that additional hospitals will be included with the aim of establishing nation-wide reporting. The project is an outgrowth of a voluntary pilot study carried out during the past four years in co-operation with the American Association of Medical Record Librarians, the American Society of Hospital Pharmacists, the American Medical Association, and the American Hospital Association.

The program is designed to develop information promptly on the untoward effects of drugs, especially the newer drugs. The information will be utilized by FDA in the resolution of medical and administrative problems under the Federal Food, Drug, and Cosmetic Act.

Prior to release for general use, new drugs are required to be evaluated from the standpoint of safety by the Bureau of Medicine of the Food and Drug Administration. Notwithstanding a most careful check of the submitted data, wide clinical use may bring to light effects not apparent in the investigative studies. When these become known, appropriate measures are taken to afford a greater degree of patient protection. Remedial steps necessary on the part of the drug manufacturer or distributor may vary from a change in the labeling, alerting physicians and others responsible for patient care, to a complete removal of the drug from the market.

The Food and Drug Administration has previously had to rely on the published literature and sporadic reports from physicians, institutions and pharmaceutical manufacturers to supplement its own small staff in following up on experience with new drugs.—U. S. Department of Health, Education and Welfare, Food and Drug Administration, Washington 25, D. C.

CLINICAL EVALUATION OF NORISODRINE SYRUP IN ALLERGIC COUGH

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AN IDEAL antitussive preparation for treatment of asthmatic cough would have the following qualities: (1) It would provide symptomatic relief, (2) it would not depress the cough center, (3) it would tend to liquefy tenacious sputum and facilitate expectoration, (4) it would cause a bronchial dilatory effect, and (5) it would not be addicting.

A definite need exists for such an effective preparation, since prevention or relief of asthmatic cough would also tend to prevent or relieve the asthmatic attack which usually follows. Recently, a syrup* which contains isoproterenol sulfate[1-4] and calcium iodide has been recommended for relief of allergic cough. Isoproterenol is chemically related to epinephrine and ephedrine, and has been used as a powder or solution for inhalation therapy for many years. Each teaspoon (5 ml) of the syrup contains 3 mg of isoproterenol sulfate and 150 mg of calcium iodide. The latter ingredient was included by the manufacturer because it is known to have a liquefying action on viscid secretions.

In a preliminary trial, the syrup was given to eight patients with troublesome cough accompanying bronchial asthma. All reported good subjective relief and none experienced any untoward reactions. Because of these encouraging observations, it was decided to conduct a more detailed study in order to determine the usefulness of this new preparation in controlling cough and bronchospasm associated with allergic conditions.

MATERIAL AND METHODS

Selection of patients for this study was made from those seen in our office or in the Allergy Clinic of Hermann Hospital, Houston, Texas. A persistent, allergic cough was the only criterion for their selection. Age, sex, or other factors were not taken into consideration.

The double-blind technique was used. Each patient was furnished with four identical bottles, each of which contained an equal volume of liquid. Every effort was made to insure that the contents of the four containers could not be distinguished except by labels with the code letters, A, B, C, or D. Two bottles contained placebos and two contained the active ingredients of the syrup. The actual contents of the containers were unknown to the patient or to the investigators until the study was completed.

Each patient was given instructions to use all the material in a single

From the Allergy Clinic, Hermann Hospital, Houston, Texas.
*Supplied as Norisodrine® Syrup, Abbott Laboratories, North Chicago, Illinois.

TABLE I. DOUBLE-BLIND STUDY: RELIEF OF ALLERGIC COUGH WITH PLACEBO AND ISOPROTERENOL SYRUP

Response	No. of Patients
Relief Using:	
All Preparations	10
Placebo (Preparations Labeled A or D)	8
Isoproterenol (Preparations Labeled B or C)	30
No Relief	1
Total	49

container before opening another. However, if it became obvious to the patient that his symptoms were not being alleviated, he was instructed to discard the remainder of the opened bottle and begin treatment with another.

The dosage prescribed varied according to the age and/or weight of the individual. As a rule, patients under three years were given one-half teaspoon every three to four hours. If they were between the ages of three and ten, instructions were given to administer one teaspoon every four hours. Those over ten years were instructed to take one or two teaspoonfuls every four hours. Other medication, for example, an antibiotic, was prescribed when clinically indicated.

Patients (or parents, if the patient was very young) were asked specifically to report degree of relief, side effects, size and frequency of dose needed to obtain relief, duration of relief, and whether they liked the taste of the preparation they were taking.

RESULTS OF THERAPY

Of the forty-nine patients included in the study, ten received relief from all preparations, eight from preparations coded A or D, thirty from preparations coded B or C, and one no relief from any preparation (Table I). Two patients developed an iodine rash while on the preparation coded B. In no instance was therapy discontinued because of side effects.

After completion of the study, the code was broken and it was found that bottles labeled A or D contained a placebo. Those labeled B or C contained the isoproterenol sulfate with calcium iodide.

DISCUSSION

Isoproterenol is one of the most effective drugs known for relief of bronchospasm and allergic cough. Traditionally, it has been administered by means of a nebulizer or aerohalor. When this route is used, relief of symptoms is almost instantaneous and side effects are minimal.

Difficulties arise in attempting to treat very young patients by means of inhalation therapy, however. Injections of isoproterenol cannot be used as an alternate route since systemic absorption of the drug results in such distressing side effects as tachycardia, palpitation, or rise in blood pressure.

Isoproterenol may be easily administered to children by the oral route, however, when the syrup is used. As shown by this study, therapy is not accompanied by side effects typically seen after injections of the drug.

The usefulness of isoproterenol sulfate syrup is not limited to children. Even though the patient may be old enough to use intelligently aerohalors or nebulizers, it is the opinion of the investigators that inhalation therapy should be reserved for relief of severe attacks. For routine use or relief of mild symptoms, both children and adults should use the syrup form of isoproterenol.

A not unexpected finding in this study was that several patients obtained relief from placebos. Quite frequently simple syrup will produce minimal relief of short duration in cough produced by upper respiratory infections. However, in all patients with cough due to asthmatic bronchitis, subjective improvement was noted only when the active ingredient was being used.

CONCLUSIONS

Isoproterenol sulfate syrup with calcium iodide is a useful adjunct in the treatment of allergic cough. In addition, it was subjectively observed to have a marked bronchial dilatory effect which reduced bronchial spasm. The calcium iodide content is adequate to promote liquefaction of thick, tenacious secretions within the respiratory tract. Therefore, this preparation meets most the criteria set up for an ideal antitussive drug.

SUMMARY

A double-blind study was conducted with forty-nine patients to determine the effectiveness of isoproterenol sulfate syrup in relieving allergic cough and bronchospasm. Ten patients were relieved of symptoms by all preparations used, eight by placebos, thirty by isoproterenol sulfate syrup, and one patient did not receive relief from any preparation. The syrup was particularly convenient for treating very young patients unable to manage inhalations, and for relieving mild symptoms in patients of all ages.

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NEW ORDER OF THINGS

"There is nothing more difficult to take in hand, nothing more perilous to conduct, or more uncertain in success, than to take the lead in the introduction of a new order of things. The innovator has for enemies all those who have done well under the old conditions, and luke-warm defenders in those who may do well under the new."—Niccolò Machiavelli, 1469-1527, *Discourses.*

SWELLING OF THE FINGERS AND THEIR JOINTS AS A MANIFESTATION OF ALLERGY

MAXWELL SPRING, M.D.
Bronx, New York

AN ALLERGIC reaction manifested primarily or predominantly on the phalanges is uncommon. In addition to the previously documented cases,[1] I am reporting three more observed in private practice in order to direct again attention to this syndrome which may occur alone or in combination with other manifestations of allergic sensitization.

Of these six cases, five patients were seen in my private practice between 1954 and 1960. In the first three patients, drug sensitization was the etiology of their allergy. Of the three patients to be described in this paper, the allergy was probably due to drug sensitization in one, but the cause of allergy in the other two is unknown.

CASE REPORTS

Case 1.—G. C. W., a thirty-year-old white man, building superintendent, consulted me on October 6, 1955 because of swelling and tightness of two weeks' duration of his fingers. He reported that his knees also felt as though they were swollen and stiff. There was no history of a respiratory infection, drug ingestion or allergy. He had been seen by me many times previously for minor complaints. At no time was any allergic manifestation observed. On examination, it was found that the fingers were slightly swollen and a ring on the third finger of his right hand was tight. The condition of his fingers suggested an allergic etiology. Epinephrine hydrochloride (1:1000) 0.3 cc was given subcutaneously with prompt relief of the stiffness and swelling.

Case 2.—K. P., a twenty-six-year-old married white woman, first noted her symptoms at the age of eighteen. These occurred every three to four weeks, first in one hand and then in the other and occasionally in both. These symptoms had the following sequence: The tips of her fingers became red and hard; the remainder of her fingers felt stiff. This state lasted twenty-four hours, after which the fingers, interphalangeal joints and wrists swelled. Any rings on the fingers felt tight. The stiffness remained in the fingers, and she was unable to use them well. After twenty-four hours of stiffness, the swelling disappeared spontaneously, and the fingers and wrists returned to normal. Occasionally, after the swelling disappeared from the fingers, there was an extension of the swelling up to the elbow and even the shoulder, with sparing of the elbow and shoulder joints. A year between her two pregnancies was one of absolute freedom from attacks. I first saw the patient for this complaint on February 11, 1957. At that time, she was in her fifth month of pregnancy. The right fore-arm was swollen. This swelling had been preceded by the typical cycle in the fingers. On examination, it was found that this arm was one and one-half times larger in diameter than the left. There was free motion in all of the joints. No axillary glands were felt. Brawny induration was present in the fore-arm and

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upper-arm. These were not tender and there was no evidence of any inflammation. The swelling appeared to be allergic in nature since no other cause such as phlebitis or cellulitis was evident. Epinephrine hydrochloride (1:1000) 0.3 cc was given subcutaneously. A marked reduction of the swelling and relief of the stiffness occurred within a few minutes. Chlortrimeton® repetabs 8 mg b.i.d. were prescribed. The next day the swelling was completely gone. She had used this drug for subsequent attacks with fair relief of symptoms. In August, 1958, she developed the typical symptoms of ragweed pollenosis, which was proven by skin testing. She was delivered spontaneously of a second baby on December 12, 1958. On December 17, 1958, she complained of the onset of stiffness in her fingers. The pads of her fingertips were reddened, non-tender and brawny. There was no swelling of the fingers or interphalangeal joints. Epinephrine hydrochloride (1:1000) 0.3 cc brought almost instantaneous relief of her symptoms. The redness disappeared and the fingertip fat pad softened considerably. She was given pyribenzamine hydrochloride 25 mg t.i.d. orally. There was no recurrence of her complaint during the remainder of her post partum hospital stay.

The patient had no hives and used very little make-up. There was no drug ingestion of any kind. The cause of her allergy is obscure.

Case 3.—F. J., a twenty-four-year-old Negro woman, was first seen by me on July 5, 1956 because of vaginal bleeding. A diagnosis of threatened abortion was made and she was given ergotrate orally. This medication diminished her vaginal bleeding temporarily. However, she continued to bleed and when next seen on September 14, 1956, she showed evidence of a severe secondary anemia. The hemoglobin was 5.1 grams and the red blood count 1.4 million. She was placed on ferrous sulfate gr. 5 t.i.d. and Unicap® Therapeutic* (Upjohn) one capsule daily after hospitalization, for a blood transfusion was refused. On this medication the hemoglobin and red cell count rose and when she was next seen by me on October 20, was found to be normal. At this time she stated that since October 18, her fingers and toes were swollen and her wedding band was very tight on the third left finger. Epinephrine hydrochloride (1:1000) 0.5 cc was given subcutaneously. Marked relief of her symptoms and disappearance of the swelling occurred within a few minutes after the injection. Chlortrimeton repetabs 8 mg b.i.d. were given. These were effective in relieving her symptoms for a short time only. When next seen on November 19, 1956, the allergic manifestations were still present in the fingers and toes. Again these were promptly relieved by Epinephrine Hydrochloride 0.2 cc of a 1:1000 dilution. Unicaps and Ferrous Sulfate were discontinued. She next returned for a checkup on January 8, 1957. After the last visit the swelling of the fingers and toes had disappeared but recurred. Chlortrimeton promptly relieved her symptoms. She was restarted on ferrous sulfate without a recurrence of symptoms. Thus some ingredient present in Unicaps was possibly the responsible agent for her allergic manifestation. However, she did not return to the office in order for me to prove this thesis.

DISCUSSION

The manifestations presented by the patients described were probably allergic in nature. The best argument for this belief is their dramatic response to epinephrine by a marked reduction in symptoms and signs. The allergic manifestations were probably of the non-reaginic type. Al-

*Unicap (Upjohn) contains Vitamins A,B_1,B_2,C,D. Calcium, Pantothenate, Nicotinic acid, Pyridoxin, B_{12}, Folic acid, Cobalt, Copper, Iron, Manganese, Zinc, Potassium, Iodine, Calcium, Magnesium and Molybdenum.

though the causative agent for the allergic responses were different, and in some cases could not be positively established, similar reactions were produced. The fingers and their joints were apparently the most reactive parts of the body and acted as "shock organs." Further investigation as to the cause of the allergic reaction is desirable in cases of this kind.

CONCLUSIONS

Three patients who manifested an allergic response confined predominantly to the fingers were described. Unicap therapeutic vitamin (Upjohn) was suspected as a cause in one patient. In the other two patients, the cause of the allergic sensitization remained unknown.

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STATISTICAL VALIDATION

Statistical validation is not an unchallengeable seal of approval. Statistics should be used only where it is useful, for an analysis of the data collected. It is the actual data, not the statistical validation, which prove the point, and no amount of statistical analysis can clarify an issue clouded by a poor experiment or muddied by contaminated data. At best, statistical analysis merely indicates the probability that differences which have been noted are not accidents of chance. When a difference has not been noted, statistical analysis very rarely indicates whether equality does in fact exist. Statistical analysis does not determine whether the data are good, bad, or indifferent, relevant or irrelevant to the issues involved, or, for that matter, worthy or unworthy of statistical analysis. In no case do they substitute for a searching analysis of the method used to collect them and of the logic behind the conclusions drawn from the collected data. The refusal of some to consider the need for statistical analysis of data in an experiment is no worse a crime than the willingness of others to swallow statistically approved conclusions without an examination of the quality of the data analyzed and of the method as a whole.—Walter Modell, "The Ethical Obligations to the Nonsubject," an editorial in *Clinical Pharmacology and Therapeutics*, 1:137 (March-April) 1960.

PRESIDENTIAL ADDRESS

CECIL M. KOHN, M.D., F.A.C.A.
Kansas City, Missouri

SERVING YOU as President for the past year has been a great privilege and an honor for which I am most grateful. For those of you who aspire to this office, I should like to advise you that it is not an honorary position. It entails much work and time and sacrifice. It requires many important decisions that must be made speedily and therefore frequently without consultation with your Board of Regents. I have endeavored in the past year to follow through with all suggestions made to me in a very voluminous correspondence from the general membership and members of the various committees. Much time has been spent in correspondence with various organizations with whom we are allied. This includes the International Association of Allergology, the Allergy Foundation of America, the American Medical Association and many others. It has been a most instructive and enlightening and pleasant year, but, frankly, I know it will be a pleasure to return to the routine practice of allergy.

A Presidential address should be a report to the general membership of the activities of the College in the past year; its aims, objectives and accomplishments, and should also include some suggestions for the future, based upon your President's experience during his term of office. I should like, therefore, to relate to you some of the activities of the past year.

The College is composed of many committees, some of which are actively functioning and some of which are relatively inactive. This year an attempt was made to activate some of these committees by contacting the various chairmen and asking them if they would accept new members. By and large, most committee chairmen were happy for these suggestions, but unfortunately this was not true in all cases. Since it is by By-Law the prerogative of the President to appoint both committee chairman and committee personnel, I have recommended to my immediate successor that he and his Board of Regents set up machinery by which participation in committee activities, both as chairmen and members, be thoroughly studied and that all non-functioning committees be reactivated, either by new chairmen or a change in committee membership. I have also suggested that committee chairmen who feel that the activity of their respective committee would be enhanced by the use of some College funds, present budgets to the finance committee for approval. This has been done by many chairmen.

Presented at the Sixteenth Annual Congress of The American College of Allergists, Miami Beach, Florida, February 28, 1960.

This year a new committee on Bronchopulmonary Physiologic Therapy was created under the chairmanship of Dr. Clifford H. Kalb of Milwaukee, Wisconsin. Its membership includes a very distinguished group in the field of bronchopulmonary therapy, and I am sure you will hear much of the work of this committee in the future.

You are, of course, familiar with the action of the By Laws Committee and your Board of Regents, concerning the new amendments in which the duties and functions of the Technological, the Audio Visual, the Publicity and the Education Committee have all been spelled out, by changes in our by laws. The Audio Visual Committee, whose chairman is Dr. Henry D. Ogden, of New Orleans, Louisiana, has as one of its functions, the establishment of a college library of films and slides that have to do with diagnosis and treatment of allergic disorders. It is hoped that within the near future, an announcement will be made notifying the membership of the availability of these films and slides for their use in teaching and lecturing.

The Education Committee, which is ably chaired by Dr. Morris A. Kaplan of Chicago, Illinois, supplants the old Public Education Committee and will concern itself primarily with undergraduate, graduate and postgraduate education in the field of allergy. This is in line with the suggestions made by my immediate predecessor, Dr. Merle Moore, in his Presidential address, last year. You may recall that one of the objectives he stressed, was that there be more education in the field of allergy. It was his desire that a continuing survey of undergraduate and postgraduate education in allergy be developed. The coöperation of joint committees on education of the two national allergy societies was envisaged. It is my hope that this committee will endeavor to carry out the suggestions made by Dr. Moore.

The Publicity Committee, which is chaired by Dr. Lawrence J. Halpin, of Cedar Rapids, Iowa, will now have complete supervision of the preparation and distribution of all news releases, medical information, and other data growing out of, or having to do with, any and all college activities, including meetings and conventions. Here again, this committee will be able to follow through on the second objective discussed by Dr. Moore last year; namely, more and better information for the public. It is hoped that through this committee we will have more accurate and interesting publicity in the field of allergy.

This year, under the direction of the Committee on Technology, a new organization to be known as the Technician's Circle has been formed. Through this Circle it is hoped that a program will be made available for all technicians who will attend future meetings. This program will be geared to the scientific level of the average technician and will be conducted during the evenings of the Instructional Course so that the technicians may attend both the Instructional Course and the meeting of the Circle itself. I am sure that this will be an incentive for many of you

to bring your technicians with you so that they may avail themselves of all of the newer techniques.

The Credentials Committee has done a splendid job. It is not an easy task to process 100 applications for membership and promotion. It requires much correspondence with members of the committee, with Fellows in the immediate locale of the applicants, and finally circulation of the Board of Regents and the President. We are grateful to those men of the Credentials Committee who have worked so faithfully.

It is my hope that many more of the general membership will participate in Committee activities. It is my feeling that new blood will tend to activate those committees that are now relatively inactive and that those committees now active, will thus enjoy a new resurgence of activity.

In general, most committees have functioned well and I am grateful to all of the chairmen and members of these committees for their assistance and diligence during the past year.

The International Association of Allergologists will sponsor the Fourth International Congress of Allergy at the Commodore Hotel in New York City, October 15 to 20, 1961. An outstanding program of symposia, panel discussions and papers is being planned to include the broad aspects of hypersensitivity, in addition to clinical allergy. An attendance of approximately 1500 physicians and a fair number of guests is anticipated. Both the American College of Allergists and the American Academy of Allergy are contributing equal amounts to this international event. The United States Public Health Service has made available a grant of $25,000 towards the expenses of this Congress. The balance needed will be obtained in grants from various commercial houses.

The International Association of Allergologists plays a most important part in the international exchange and the spread of knowledge in the field of allergy and in the area of international good will. We are the hosts this time for the Fourth International Congress and are anxious to leave a good impression on our foreign visitors, one worthy of American friendship, generosity and coöperation. Many members of the College will not only present papers and participate in the panel discussions and symposia, but will serve on key committees. For example, the American Physicians Committee is chaired by Dr. Lawrence J. Halpin of Cedar Rapids, Iowa. The Banquet and Entertainment Committee is under the chairmanship of Dr. Howard G. Rapaport of New York City. Dr. Ethan Allan Brown of Boston, Massachusetts, is chairman of the Editorial Committee. Dr. Murray M. Peshkin of New York City is Treasurer of the Organization Committee. Many members have been asked to serve on committees, and I know that all of you will do everything to make the Congress the finest that the International Association of Allergologists has ever sponsored.

This month the decennial meeting of the White House Conference on Children and Youth will be held in Washington, D. C. A concerted effort

has been made to have the allergic child as a subject on the Agenda of this Conference. Dr. Howard G. Rapaport of New York City and Dr. Boen Swinny of San Antonio, Texas have been appointed official representatives of the College.

The Allergy Foundation of America, although a relative newcomer to the ranks of voluntary health agencies, has developed a well-rounded program of both professional and public services. It supports a scientific investigation, provides information and educational materials, both for the profession and the public, and promotes community services for the allergic patient. This type of program requires financing and your Board of Regents has voted again to support their efforts. We should all remember that a program of the nature and magnitude of that of the Allergy Foundation requires a relatively large amount of money. Since allergies are not for the most part "killing diseases," support from the public in general is not apt to be as generous as with other diseases. Those people who have an allergy or an allergic child or relative, are clearly aware of the importance of the allergic diseases. These are the people in your communities who should be urged to give financial support to this Foundation. Each of us should also financially contribute since this increased scientific program and increased public education program will be of benefit to all of us.

I should like to call your attention to the new face of the ANNALS OF ALLERGY. Your Board of Directors, at its interim meeting, approved the new cover design, which streamlines and modernizes our Journal. You have been made aware of the fact that the ANNALS OF ALLERGY has become a monthly publication. Since its inception in July, 1943, the ANNALS has been a bi-monthly publication. The monthly publication has been accomplished with no increase in membership dues. It will mean that the membership will enjoy many more excellent papers and there will be a much shorter period between submission of papers and their publication.

By action of your Board of Regents, beginning in 1961, no registration fee shall be charged to Associate Fellows and Fellows of the College, in good standing, who wish to attend the Graduate Instructional Course. I am sure this will please the membership.

I should like to report to you concerning the results of the mail vote of the membership regarding a change of our meeting date. It was the opinion of your Board of Regents that the percentage of answers received did not indicate that a change from the March-April schedule should be made, and it was therefore decided that these annual meetings would be continued in the Spring. We already have finalized dates for the 1961 and 1962 meetings in the Spring. The meeting to be held in Denver in 1963 will, therefore, be held in the Spring, and future convention dates will be made for the same Spring period.

The annual meeting of the American Medical Association, which will be held in Miami Beach in June of this year, will again have an Allergy

Session as part of its total program. This Session is jointly chaired by the President of the American Academy of Allergy and the President of the American College of Allergists. This year it was the privilege of the College President to appoint the secretary for this session. Dr. Jack Rudolph of Miami Shores, Florida, received this appointment and I am pleased to inform you that an excellent program has been arranged for the Session. I would like at this time to express my sincere appreciation to Dr. Rudolph for a job well done.

The Women's Auxiliary, under the presidency of Mrs. J. Warrick Thomas of Richmond, Virginia, has continued to function in its usual excellent manner. We of the College are exceedingly proud of our auxiliary. Its numerous activities help to occupy and entertain our wives while we are busy in our scientific sessions. We are also grateful to this fine organization for its generous contributions to the College. Our Bela Schick Award and the Clemens von Pirquet Award are annually donated by your Women's Auxiliary. The Auxiliary also grants scholarships to the Instructional Course for worthy individuals, particularly those who are working at colleges and universities. It was most gratifying to me, as President, to notify your Board of Regents this year, that the Women's Auxiliary donated the sum of $1,000 to the Saguaro School of Tucson, Arizona, and the sum of $750 to the Association of Allergists for Mycological Investigation.

One of the outstanding features of the College has been its keen appreciation of the need of postgraduate education, and it was at the first annual meeting of the College in 1944 that the first postgraduate instructional course in Allergy was held. This has been continued annually since that time. This year our instructional course had a most outstanding group of instructors, and the very large enrollment of students attests to its value. The instructional course was under the direction of Dr. G. Frederick Hieber of St. Petersburg, Florida, and I should like to express my thanks to him for a job well done.

The excellent program which we have had at the annual Congress this year was under the able direction of our President-Elect, Dr. Giles A. Koelsche of Rochester, Minnesota, and I wish to express my sincere thanks to him for the general excellence of the presentations.

I should also like to thank all the participants, both in the instructional course and in the scientific sessions. The success of our meetings may be attributed to the excellence of their respective endeavors.

I am most appreciative for the advice and counsel I have received from our Executive Vice President, Mr. Eloi Bauers. His efforts for the College have been untiring. These beautiful surroundings and excellent service we are receiving here at the Americana have been brought about by his efforts. Our commercial and scientific exhibits are all under his general supervision. He has faithfully attended and advised us at all meetings of the Board of Regents, the Board of Directors, the Finance Committee,

the By Laws Committee, as well as at our own annual business meetings. He has given unstintingly of his time for the College. For all of this, I would like on behalf of the Officers, the Board of Regents and the membership, to express to him our sincere appreciation.

I am also grateful to our Treasurer, Dr. John D. Gillaspie, for his untiring efforts. In addition to acting as Treasurer of the College, Dr. Gillaspie conducts all of the affairs of our home office in Boulder, Colorado. All mailing that emanates from our Boulder office is under his direct supervision. I should like for all of you to know that as of January 1, 1960, Dr. Gillaspie retired from the active practice of medicine and will now be devoting almost all of his time to College affairs. I wish at this time to also express to him the sincere thanks of the Officers, the Board of Regents and the general membership.

Your Board of Regents has been a most active and inspiring group to your President. I have frequently called upon the Regents for advice and approval of many matters that have arisen in the past year. Their replies have been immediate, and major credit for the accomplishments of this year should go to them.

Your Board of Directors has spent many hours in discussing College matters at its interim meeting. Directors, too, have given of their time far beyond the usual call of duty.

We are all grateful for the excellent accommodations, service and entertainment that has been made available to us by the Americana Hotel. We are also appreciative of the beautiful weather that Florida has given us during this past week. As of this moment, it is the one location on the eastern seaboard of the United States that gives us the kind of weather that is required for a successful convention, and if we were at any other point we would all be snowbound and unable to move in the direction of our respective homes.

And now, it gives me great pleasure to turn the gavel of the Presidency over to Dr. Giles A. Koelsche of Rochester, Minnesota.

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PREDICTION AND THE PHYSICAL WORLD

"In agreement with the Heisenberg uncertainty principle, we now see that a complete knowledge of the state of a physical system at any given instant is not sufficient to permit an exact prediction of that system's future behavior. The best that we can do is to make statistical calculations concerning the future behavior that can be expected on the average. As a consequence, we now have to regard the true connection between physical cause and effect as a statistical one and give up the idea that the behavior of the physical world is strictly determined."—Richard C. Tolman, "A Survey of the Sciences," *Science*, August 15, 1947.

In Memoriam

LEE PETTIT GAY, M.D., F.A.C.A.

Doctor Gay was born in Leeper, Missouri, on August 2, 1894. He received his A.B. degree from the University of Missouri in 1916 and his M.D. from the Washington University School of Medicine in St. Louis in 1918. He was in France in World War I serving with Base Hospital Unit No. 1. From military service he went to St. Louis where he practiced internal medicine and allergy.

He was a member of Cole County Medical Society, St. Louis Medical Society, and the American Medical Association. He was a Fellow of the American College of Physicians and a member of the American Academy of Nutrition. As a member of the Missouri Historical Society and the University Club, he was active in many affairs.

Doctor Gay was the author of many papers on the subject of nonreaginic food allergy and at the time of his death he was in Barcelona to present a paper before the European Allergy Society on this subject. Besides his widow, Mrs. Frances Hays Gay, he is survived by his brother, Dr. George W. Gay of Ironton, Missouri.

Doctor Gay was promoted to Fellowship in The American College of Allergists in 1945.

News Items

THE CHICAGO SOCIETY OF ALLERGY

The Chicago Society of Allergy elected the following officers for the year 1960-1961:

President.....Bert B. Schoenkerman, M.D.
President-Elect.....Charles M. Jenkins, M.D.
Secretary-Treasurer.....Abe Matheson, M.D.

THE CANADIAN ACADEMY OF ALLERGY

At the annual meeting of the Canadian Academy of Allergy, the following officers were elected:

President.....J. Leger, M.D.
Vice President.....J. H. Toogood, M.D.
Secretary-Treasurer.....H. Bacal, M.D.

THE BUFFALO ALLERGY SOCIETY

The Buffalo Allergy Society announces that its new officers for 1960-1961 are:

President.....Thelma Brock, M.D.
Secretary.....Leonard Wolin, M.D.
Treasurer.....George B. Rosenfeld, M.D.

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"... the work horse of the [antihistamine] group ... effective ... well tolerated ... especially convenient for the busy patient...."

· Rogers, H.L.: Postgrad. Med. 26:85.

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- simple dosage schedule produces rapid, reliable tranquilization without unpredictable excitation
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- No barbiturate depression
- No suppression of adrenal function

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For 24 hour control: For adults 45 cc. doses before breakfast, at 3 P.M., and before retiring; after two days, 30 cc. doses. Children, 1st 6 doses 0.3 cc.—then 0.2 cc. (per lb. of body weight) as above.

1. Schluger, J. et al.: Am. J. Med. Sci. 233:296, 1957.
2. Bradwell, E. K.: Acta med. scand. 146:123, 1953.
3. Truitt, E. B. et al.: J. Pharm. Exp. Ther. 100:309, 1950.

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